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ONNARCOTIC DRUGS FOR THE RELIEF OF PAIN AND THEIR MECHANISM OF ACTION*

Consulting Editor and Conference Chairman

FRANK M. BERGER

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THE PURPOSE OF THIS MONOGRAPH

F. M. Berger
Wallace Laboratories, New Brunswick, N. J.

A large number of new therapeutic agents introduced during the past twenty thirty years have been used with great success in the treatment of many dis- ses and symptoms. Some of these are the sulfonamides, the antibiotics, the ıtihistaminics, the ganglionic blocking agents, the centrally acting muscle laxants, the corticosteroids, and the tranquilizers. There are many others. is strange, indeed, that so little progress should have been made in the field analgesics. The most important drugs in this field, such as morphine, aceto- ıenetidin (phenacetin) and acetylsalicylic acid (aspirin) were introduced be- re the beginning of this century and have been in widespread use ever since. ınumerable modifications of these basic compounds have of course been made, ıt there is some doubt that any of these derivatives possesses important ad- ıntages over the parent substances.

There are many reasons for the lack of progress in this field. Perhaps the ost important are our ignorance of the fundamental physiology of pain and e absence of specific and reliable methods for its measurement.

The physiologist's concept of pain has been well expressed by Sherrington 947), who defined physical pain as "the psychical adjunct of an imperative otective reflex." This definition does not satisfy the clinician, who observes at pain does not always accompany protective reflexes (think, for instance, psychogenic pain), and that protective reflexes are not necessarily the pre- rsors of painful sensations. As yet, it has been impossible to account for the ıried clinical manifestations of pain in terms of specific neural structures ꞏeele, 1957). It appears clear, however, that pain cannot be a pure or specific nsation, because there are so many kinds of it. Pain, as most other sensa- ons, must be the result of an integration and abstraction of peripheral stimuli the central nervous system. The key to the problem is to understand how imuli are translated into perceptions or sensations, but neurophysiology has information to give us on this (Livingston, 1943).

The measurement of pain and the evaluation of analgesic agents that are so osely allied with it are still being discussed. In animals, the milder pain-re- ving drugs, such as aspirin, are usually evaluated by the ability to lower ver, to prevent writhing, or to prolong the duration of local anesthesia. ıese tests may not be correlated to the analgesic power of these agents. The ore powerful narcotic analgesics are evaluated in animals by measuring their ility to suppress the natural protective reflexes to mechanical, electric, or ermal stimulation. These tests measure the reaction threshold but not the in threshold. In man we can differentiate between existing or pathological in and pain that has been experimentally inflicted. Beecher (1957) and cer- in other experienced observers believe that in man the experimental pain tech- ques generally employed at present are probably useless for the appraisal of algesic agents, and that assay of the analgesic power of drugs can be carried t only when pathological pain is employed. Why this should be the case is not clear, and it may simply mean that sufficient care and trouble have not been spent on the development of a suitable technique.

All drugs that relieve pain can be divided into three large groups. The first comprises drugs that modify the perception of stimuli at the pain-receptor sites. The agents of the second group modify the central perception of pain and those of the third group change the reaction of the individual to the pain experience.

The first group of agents remove the pain-producing effect of peripheral stimuli. This can be done by making the pain receptors insensitive to pain, as is the case when toothache is relieved by infiltrating the area around the tooth with a local anesthetic or by altering in some way the state of tissues in which the pain receptors are located, as when pain due to smooth muscle spasm is abolished by the administration of atropine. It may well be that aspirin, phenylbutazone, and certain other analgesics affect neither pain perception nor reaction to pain, but relieve pain by producing effects in the periphery.

There is much uncertainty whether any of the available analgesic agents can modify pain perception without at the same time altering the reaction of the individual to the pain experience by producing changes of mood and consciousness. Beecher (1957), in his thoughtful review, concludes that analgesic agents appear to exert their principal, if not entire, effect on the "reaction component" rather than on the "original sensation." Morphine and the synthetic analgesics that are chemically and pharmacologically related to it, as well as alcohol and the anesthetics, undoubtedly have a marked effect on the psychic reaction to pain, but it is not clear to what extent they affect perception of pain.

A substance that would change perception of pain without affecting the reaction to it would clearly be of great scientific and practical interest. Such a substance would raise the threshold of pain perception without affecting the threshold to pain reaction. Such a substance might not be addicting, as it would not necessarily affect the mind and would not produce euphoria.

The working of the autonomic nervous system was largely elucidated because of the availability of certain drugs that produced selective effects at certain well-defined sites. It may well be that, in a similar manner, new analgesics with selective sites of action could be of great assistance in elucidating the physiology of pain. Such substances will not be easy to recognize, since they may be rejected by the pharmacologist because they may not prove active in the accepted assay procedures. When clinically evaluated on patients suffering from different kinds of pain, they will be very effective in some cases and completely ineffective in others. They may thus be easily overlooked and discarded as worthless when the results are evaluated on a statistical basis, using double-blind procedures. The effects of the drug, however, will be noticed if each patient is evaluated individually.

There is no need to stress the importance of research in this field. Most patients who come to see a doctor complain of pain and demand relief from it. Many kinds of pain cannot be satisfactorily relieved at the present time, and the available remedies cannot be used to the best advantage because their mode of action is not fully known.

The purpose of this monograph is to focus attention on this field and to stimulate research in it. These sentiments have been well summarized by Jenkins

Stevens' *Handbook of Experimental Psychology*, from which, in closing, I uote:

"In summary, then, it seems that we actually know little or nothing about hat simple qualities are both sufficient and necessary for the various complex mesthetic perceptions. This does not imply that the complex phenomena re unique or unanalyzable, or that there are additional sense organs remaining be discovered. It does mean that the complex somesthetic perceptions are a ch and almost untouched field calling for further research."

References

EECHER, H. K. 1957. The measurement of pain. Pharmacological Rev. **9:** 59–209.
EELE, K. D. 1957. Anatomies of Pain. Thomas. Springfield, Ill.
ENKINS, W. L. 1951. *In* Handbook of Experimental Psychology. S. S. Stevens, Ed. : 1188. Wiley. New York, N.Y.
IVINGSTON, W. K. 1943. Pain Mechanisms. Macmillan. New York, N.Y.
HERRINGTON, C. 1947. The Integrative Action of the Nervous System. : 292. Cambridge Univ. Press. Cambridge, England.

THE PHYSIOLOGY OF PAIN

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A decade ago I had occasion to review the problem of pain in an article[1] that was not noticed by many neurophysiologists. In looking over more recent literature I was pleased to find that the kind of approach and picture that I then suggested remains essentially valid, despite considerable additions to our knowledge of the pain pathways, chiefly within the central nervous system. The material presented here is based on my earlier review,[1] supplemented by a later, more general one,[2] and by Sweet's chapter on pain in the *Handbook of Physiology*.[3] Other recent reviews are the Ciba Foundation monograph[4] and Barber's article in the *Psychological Bulletin*.[5]

The lack of real advance in new understanding, including learning how pain emerges into consciousness, is not due to any lack of importance of the subject or of interest in it. I remember well my experiences as an intern at Los Angeles General Hospital, Los Angeles, Calif., over one third of a century ago. We had many Mexican patients, and the only words of Spanish that I learned, I regret to say, were "*Donde duele?*,"* which sufficed. The essential point that I shall emphasize, one already alluded to by other contributors to this monograph, is the very real difference between awareness of pain and suffering from it. This distinction is of major importance clinically and pharmacologically, and we are now fairly close to understanding it neurophysiologically.

It is possible, on stimulating pain afferents by applying painful stimuli, to produce reflex responses such as changes in skin resistance at intensities below those required to produce any conscious awareness of them. Conversely, with stronger stimuli or other conditions, one can obtain a perfectly clear awareness of pain and yet not be particularly distressed by it. This condition can be achieved, for example, even with very severe pains, by procedures such as frontal leukotomies or topectomies. The sufferer with causalgic pain and allied ills may remain perfectly aware of feeling severe pain, but may no longer be really distressed by it; probably morphine acts in this manner. Although somewhat debatable, the best evidence I know of indicates that morphine does not raise the threshold of pain receptors to peripheral stimulation. The messages come into the nervous system as before, but they no longer seem as important as formerly.

There is, of course, a tremendous variability in the reaction of a given individual to a given painful stimulus, depending upon what can be called, loosely, the internal emotional state and the total external input (aside from the pain stimulus). This variation involves some of the mechanisms that I shall discuss. I suspect that the reader has had the experience of a toothache that seemed insufferable in the forlornness of late night, but became relatively minor the next morning, especially when facing the dentist's chair. Conversely, in the intense emotion of battle, only about one third of the soldiers who are severely wounded require analgesic medication whereas, in the same age group of males in civilian ife suffering less severe trauma in surgical operations, 80 per cent do require uch drugs. Let us examine the mechanisms involved.

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* "Where does it hurt?"

Pain, of course, is of the utmost importance to the organism. In those rare ndividuals who lack perception of it, or when this perception is lost in disease, s in leprosy or tabes, repeated severe insults to the body occur, and major estruction results. Pain receptors are everywhere, although an occasional reiew or article still states that skeletal muscle, for example, or some of the visera, cannot give pain. The stretching of almost any tissue or organ that reists stretching can produce pain. Stretching the viscera and blood vessels is otoriously painful; conversely, their constriction, which involves contraction f the smooth muscle in their walls, also can cause pain. The same thing is rue of skeletal muscle. Anyone who questions this should recall a leg cramp, hich is also related to contraction and stretching, or listen to a description of he pain of a muscle rupture. Pain afferents from skeletal muscle, as well as nd tendons and joints, are known, and pain certainly can be elicited from joints nd by stretching muscles under certain conditions; probably the Phillipson's nd lengthening reflexes of the spinal animal are related to these pain receptors. he skin is sufficiently well known to require no further comment.

In all of these cases the sensitiveness to pain at the periphery is increased by he processes of inflammation. Whether these processes be mechanical or hemical or the pulsating effects of dilated vessels or some combination of all hese is far from known, but certainly there is a marked exacerbation of pain eceptivity from inflamed regions. This phenomenon deserves extensive study.

What neural mechanisms are involved? I know of no evidence that pain is erceived by any receptor other than a naked nerve ending. This does not ean that all naked nerve endings are pain receptors. It was long maintained, r example, that the cornea, which has only such naked endings, received only ain, but more recent evidence indicates decisively that temperature and a light ouch can also be recognized from the cornea. The same thing is true for the ardrum and other regions; indeed, the fiber groups that carry pain (the δ and fibers) also mediate other sensations. However, the receptors for pain fibers re certainly the multiple undifferentiated naked endings scattered throughout he tissues and organs of the body. In the skin and cornea, where they have een studied carefully, it is now quite certain that these endings do not constiute an interlocking syncytial network of fibers, as was once believed. A given erve fiber may serve a skin area of the order of 50 sq. cm. (5 cm. by 10 cm.), hich is a large patch of skin, but many similar nerve fibers will also enter that me region so that their peripheries overlap and interlace; however, they do ot form a continuum.

Considering next the afferent paths into the central nervous system: it is quite ell established that 2 types of fibers carry pain, although not exclusively. The -called Aδ, or δ, elevation of the action spike, described in the original oscilloope work that separated fiber types in a nerve trunk, is due to the relatively inly medullated fibers, mostly 2 to 4 μ in diameter, which conduct at a speed 15 to 20 m./sec. They constitute about one third of the total number of edullated fibers in peripheral mixed nerves and certainly carry a type of pain. hen the ending of 1 such fiber is given a single stimulus (a single electric shock ver the skin ending is effective), one gets a subjective experience usually more like a tap than a prick, but when the same spot is tetanized a clear experience of pricking pain results. The other pain afferents are among the C fibers, which are very thin, nonmedullated fibers about 1 μ in diameter and conducting at 1 to 2 m./sec., rather than 20 m./sec. There may be 4 times as many C fibers in a somatic nerve trunk as the total of medullated A fibers, and as many as 20 per cent of the fibers in a sympathetic trunk. The threshold for C fibers is as great as 100 times that of A fibers.

I stress these 2 kinds of fibers because there is no disagreement as to their existence and little as to their being related to the experience of pain. There is considerable disagreement in the literature, however, as to my next point. Many authors have described the double-pain experience after an appropriate stimulus, such as a quick, sharp pain and a slow, dull, aching or burning pain, and it has seemed reasonable to relate the rapid experience to conduction in the relatively fast δ fibers and the slow experience to conduction in the slow C fibers. Personally, I have no question about the 2 times and qualities, for I have never had difficulty in demonstrating the double pain on myself or to others (an easy method of doing this is to rest the shin on the seat of a chair with the unshod foot vertical, and give a smart rap to the sole with a flat piece of wood or a book). However, recent reviews, including that of Sweet,[3] challenge the whole phenomenon as a figment of some experimenters' imaginations. Whatever the final answers may be, this dichotomy fits well into the over-all picture, and I shall use the double-pain system throughout this discussion.

Pain messages now enter the spinal cord. Those that come along δ fibers run up the ipsilateral dorsal column, primarily in relatively large fibers, and speed along at 50 to 80 m./sec. The messages that come in through C fibers travel in the crossed ventrolateral columns, in thin fibers, perhaps 2 μ in diameter, and at a correspondingly low speed. The 2 systems of pain afferents thus continue to be quite distinctive. Indeed, the different systems have been traced into the midbrain, where they can be separately sectioned surgically; into the thalamus, with an average total conduction time (including synaptic delays) for the δ system of 8 m./sec. and for the C system of 0.8 m./sec., again about one tenth; and, finally, to the somasthetic areas in the cortex, strongly to both I and II limb areas in cats, rabbits, and dogs, mainly to the I area in monkeys. On the way up, some fine fibers carry pain messages to the reticular formation, whence other fibers "alert" the cortex.

Now that pain messages have permeated the nervous system, I must be vague as to whether pain is experienced in the cortex or in subcortical structures. Fortunately, it may not matter a great deal, because there is such a strong reverberant circuit, a double feedback connection between the cortex, the thalamus, and other deep structures that activation entering that system might have the same outcome wherever it is related to conscious awareness. The intense generalized pain of thalamic lesions (the thalamic syndrome of Roussy and Dejerine), is to be recalled here, as well as the fact that cortical stimulation produces pain only rarely, and then chiefly when pathology is present.

Let us now return to my initial point concerning 2 basically different afferent systems. These are involved not only in pain, but also in experience in general. One system, relatively diffuse and related to the tone or set in which particularized patterned sensory experience is placed, includes the C system;

the other, giving the pattern, includes the δ system. Although the terms introduced by Head and Holmes have been violently attacked over the intervening decades, I find the words protopathic and epicritic extremely convenient. The protopathic is diffuse and vaguely discriminated, is strongly tinged by affect and, tending to summate and overflow when activated, is prepotent in determining the experience and the behavior of the individual. The epicritic experience, in contrast, is discrete, particulate, and localized and gives the patterned details of an experience, but with little affect. It has been happily compared with a picture on a television screen. The epicritic messages correspond to those that give the figures; the protopathic are like those (ordinarily unnoticed by the viewer when the set is well adjusted) that determine the setting and character—sweep speed, line pattern, level of contrast, total brightness, and other such characteristics.

The really important point is that these systems are, in one sense, antagonistic and, in another, complementary. For pain, explicitly, when the epicritic δ system is active, it may produce, to be sure, a clear awareness of pain (pricking, cutting, or other defined pain), but it does not lead to great suffering; rather, it inhibits the suffering induced by activation of the C protopathic system. Conversely, when the C system is active, it leads to all the suffering aspects of pain. I like to call it causalgic pain because it has many of the attributes so clearly recognized in causalgia, related to trigger points in general, and ike aching. When this C system is active it facilitates the respones of cortical neurons to other pain impulses and whatever pain experience is involved. The epicritic system, conversely, and not only the pain but other modalities of input fibers such as those for touch and pressure, tend to suppress the protopathic-type pain.

Next, let us consider a few experimental examples of these points. That pain is associated with the excitation of something is commonplace. Vast pains arise on the stimulation of trigger points. New trigger points can be generated by irritants applied to skin regions not ordinarily involved in the pain responses. Anginal attacks normally involve the left side; if the right chest has been irritated, as by cantharides concomitant with an anginal attack, future pain attacks may irradiate to the right as well as the left. The burning pain of putting a finger into ice water spreads to other fingers, not through peripheral connections, but centrally. Pervading pain is produced by stimulation through deep electrodes of the central gray matter or other parts of the old gray matter or of the afferent pathways to them. Causalgic pain "leaks" past surgical lesions. Many other examples are cited in the earlier eview.[1] The evidence for pain on stimulation of the protopathic system is traightforward and need not be belabored.

Less familiar is evidence suggesting an inhibitory action of the epicritic system on this protopathic type of pain, but relevant data are plentiful. One of he earliest, and not unchallenged, findings was offered by T. Lewis and his coleagues. A pressure cuff on the arm produces a progressive block of peripheral nerve fibers; as conduction in the δ group disappears, the pain experienced suddenly develops a causalgic character. Lower-body ache or itch. such as pruitus ani, may be relieved by section of the the ventrolateral columns, but is everely exacerbated by section of the dorsal columns. Recently, surgical intervention in the midbrain has shown similar effects. Unilateral section of the epicritic-type paths gives a prompt hypalgesia, but in a few days there develops unilaterally a progressive burning ache that becomes agonizing and continuous.

In the periphery these systems can sometimes be manipulated to give, reversibly, pain or pain relief. The protopathic type of pain arises from the regenerating skin at an ulcer margin when only one pain fiber innervates it; when several fibers have entered, the aching type of pain disappears. A case has been reported in which, after a bullet wound in the arm, 3 different nerve trunks merged to innervate the same piece of skin on the hand; the subject had no pain or other difficulty. However, when 1 trunk was blocked by a local anesthetic, some tingling developed; when 2 were blocked, a severe causalgic pain appeared; and when all 3 were blocked, of course, anesthesia resulted. Anesthesiologists have met similar situations when using root-block anesthesia. One man, for example, had had severe amputation-stump pain 3 decades prior to an operation under spinal anesthesia. From the time the spinal roots became blocked until the anesthetic wore off he suffered agonizingly the ancient stump pain. Again, itch depends on C impulses and is relieved by rubbing, which activates δ fibers. A recent dramatic case report is comparable: a man with a continuous aching pain in the arm could always block it by squeezing the tips of his third and fourth fingers, so he kept his hand clenched to avoid pain; and this was not psychosomatic. Conditions such as causalgia and tic douloureux can often be overcome similarly by leading a patient to accept epicritic stimulation of the painful part.

The protopathic C system is the ancient, relatively undifferentiated one. It is constructed of short neurons with multiple synapses and wide connections and, probably, slow decremental conduction. These neurons possess relatively slow mobility, requiring much summation to activate them, but then give long after-discharges and long-enduring potentials. They interact through the fasciculi propriae in the central gray matter all along the primitive neuraxis; it is via such segmental paths that pain leaks past a chordotomy or similar surgical lesion of the principal pathways that were laid over the protopathic system later in evolution. Fortunately, these protopathic neurons are, on the whole, particularly sensitive to chemicals, both stimulating and depressing. The catechols, the indoles, most depressant agents, and other drug groups seem to act primarily on this system. In all these respects the epicritic elements are opposite.

With chronic states, that is the severe central causalgias, there develops what I have called a physiological inflammation. Continued and repeated protopathic inputs have built up excitation in central neurons by summation, irradiation, synchronous beating, reverberation in closed loops and, finally, fixation of a hyperactive state. As a guess, interneurons are mainly involved, but perhaps cortical pyramids, Golgi cells, and other structures participate. In any event, the elements related to pain experience become overactive and overactivable as a result of increased exciting bombardment, of decreased threshold, or of both. In both acute and chronic activation the C-fiber system acts on the pain-generating neurons to stimulate the protopathic structures directly or to sensitize them to patterned epicritic activation, presumably involving the cortex, as in the alerting responses from the reticular formation. Conversely, the δ system raises thresholds of the afferent channels so that protopathic impulses are blocked along the way.

A final few words on drug action, especially in relieving pain. A given agent may decrease the peripheral excitation and thus the afferent pain impulses. Where inflammation is involved, drugs such as the salicylates and cortisone may decrease the lesion and the pain. Where muscle spasm is the pain generator, especially if the skeletal system is involved, a relaxant can help; mephenesin and carisoprodol may contribute such an action. On the other hand, if the excitation is unchanged, the receptor threshold could be raised. This elevation is certainly, for several senses, under the influence of efferent nerve fibers, but I know of no evidence for it in the case of the simple pain receptors, nor of any drug that specifically depresses them. If pain messages reach the central nervous system, management of the condition is quite logical in principle: one may decrease protopathic flow by means of lesions or by raising thresholds of the appropriate neurons, or one may increase epicritic flow, which itself suppresses the protopathic transmission or neuron responses. In both cases the activation of the pain neurons is lessened.

At a meeting on carisoprodol held at Wayne State University, Detroit, Mich., last spring[6] I was sufficiently foolish or sufficiently rational to suggest, simply on the basis of the clinical phenomena reported, that perhaps the action of this drug is to depress the reticular formation. I am pleased to see that work reported in this monograph makes that speculation seem less wild, perhaps, than it first seemed.

References

1. Gerard, R. W. 1951. The physiology of pain: abnormal neuron states in causalgia and related phenomena. Anaesthesiology. **12:** 1–13.
2. Gerard, R. W. 1960. Molecules, neurons, and behavior. *In* Handbook of Physiology. Sect. 1. Neurophysiology. **3.** J. Field, H. W. Magoun & V. E. Hall, Eds. Am. Physiol. Soc. Washington, D.C. In press.
3. Sweet, W. H. 1959. Pain. *In* Handbook of Physiology. Sect. 1. Neurophysiology. **1:** 459–506. J. Field, H. W. Magoun & V. E. Hall, Eds. Am. Physiol. Soc. Washington, D.C.
4. Wolstenholme, G. E. W. & M. O'Connor (Eds.). 1959. Pain and Itch. Nervous Mechanisms. Little, Brown & Co. Boston, Mass.
5. Barber, T. X. 1959. Toward a theory of pain: relief of chronic pain by prefrontal leucotomy, placebos, opiates, and hypnosis. Psychological Bull. **56:** 430–460.
6. Gerard, R. W. 1959. Summary of the Conference, in The Pharmacology and Clinical Usefulness of Carisoprodol. J. G. Miller, Ed. Wayne State University Press. Detroit, Mich.

Discussion of the Paper

Chauncey D. Leake (*Ohio State University College of Medicine, Columbus, Ohio*): To begin this discussion I shall ask Gerard to comment upon the efferent system in connection with pain.

Gerard. In so far as the spinal level is concerned, of course, my first reaction is to think back to the concept of pain quoted from Sherrington by Berger: "the physical adjunct of an imperative protective reflex." This is primarily the flexion reflex. The ordinary behavioral response to that kind of pain is a defensive or an avoidance movement. Such action, of course, makes use of the same motor system as every other act, so I doubt whether there is much point in attending to the efferent side in connection with pain, in contrast to any other motor response.

LEAKE. I have not made myself clear. How about the efferent sensory factor?

GERARD. Thank you; your question brings out a point about the feedback part of the mechanism that I went over too hastily. How does the epicritic type of impulse enter the situation and tend to inhibit the other type? There are 2 possible ways for the epicritic impulse, which is faster, to block the protopathic one and I rather suspect that both methods are involved. The epicritic impulses enter the nervous system more rapidly than do the protopathic ones and thus can modify the synaptic junction to make it less transmissive for the protopathic messages. The other way is by a straight feedback mechanism, the epicritic impulses going on up to higher centers and feeding back down on one of the way stations in the afferent path and raising pain thresholds there.

In general, one can control pain, either peripherally or centrally, only by decreasing the activity of those neurons whose activity is associated with pain. There are 2 ways of doing this: first, by decreasing the inflow of messages to excite those neurons and, second, by raising the pain thresholds of those neurons so that it takes more messages than before to excite them. All drugs must act in one or the other of these ways.

QUESTION: Gerard mentioned certain terminology that, according to Lewis, would belong to deep pain. I wondered whether Gerard agrees with Lewis that there are 2 types of pain, one being skin or superficial pain and the other deep pain.

According to Lewis, skin pain is always sharp and pricking or bright, and it becomes burning only when it is longer in duration, whereas the definition of dull pain attributes it to the deep structures under the skin and thus differentiates it from skin pain.

GERARD. You are asking essentially for an anatomical separation, whereas I gave a physiological and functional one. I question if burning, causalgic pain is limited to the deep structures; such pain can also be obtained from regenerating or ulcerated skin, or under other conditions in which the epicritic fibers from the skin are thrown partially out of function.

SOME PSYCHOLOGICAL ASPECTS OF PAIN AND THE RELIEF OF SUFFERING*

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There are many important things to say about the psychology of pain and the relief of suffering, four of which are the main purpose of this paper. The first is that certain aspects of personality and perceptual style, which are changed by a prefrontal lobotomy carried out for the relief of pain, are precisely those that differentiate within the normal population those who can tolerate pain well from those who suffer greatly from it. The second point is that these differences in tolerance for pain are paralleled by other striking differences in the subjectively perceived intensity of sensation other than pain. Some persons, whose nature it is to reduce the intensity of their perceptions subjectively, can tolerate pain well. The third point is that there appear to be sex differences in this tendency to reduce the subjectively perceived intensity of sensation. Finally—and this is the fourth point—the tendency to reduce the perceived intensity of sensation can temporarily be so accentuated by drugs as temporarily to establish greater tolerance of pain.

Before going further, however, it is necessary to recapitulate some of the facts that have appeared in earlier reports.[1,2]

A first point concerns the aspects of personality that are changed by a prefrontal lobotomy carried out for the relief of pain. Surgery in the prefrontal areas of the brain so increases tolerance for pain that the patient can sleep without morphine and wake without moaning. What is remarkable about this surgery is that the source of the pain has not been dealt with, nor has the threshold for pain been altered; instead, the person experiencing the pain has been altered. The alteration in personality following brain surgery is quite specific when it achieves this effect, as earlier work with about 100 patients has demonstrated.[3,4]

Our work[2] has indicated that a person who is exceptionally tolerant of pain has the personality and perceptual style of the individual after a prefrontal lobotomy, whereas one who cannot tolerate pain resembles in personality a patient before prefrontal lobotomy. We have shown that this correlation is true with regard to pain of major surgery, minor surgery, and bronchoscopy, and that it is also true of tolerance for experimental pain as measured by the pain that can be endured *above* the threshold. This conclusion is based upon a study of 70 patients.

Satiability

Perhaps the most interesting facet of the alteration in personality and perceptual style that accompanies the relief of suffering from pain by a brain operation is an increase in what Köhler and his associates originally called satiability.[5] Briefly stated, Köhler showed that there is a tendency for some

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persons to reduce the intensity of a perception subjectively after they have been stimulated by a more intense perception. These and other investigators found individual differences in susceptibility to satiation. It is reported that susceptibility to satiation in one modality, such as vision, is correlated with susceptibility to satiation in other modalities, such as touch.[6] Satiability is increased by certain types of brain lesions.[7] Eysenck relates suceptibility to satiation to the personality dimension called introversion-extraversion; the more extraverted the personality, the greater his susceptibility to satiation.[8] My associates in London and I found that brain lesions have a selective effect upon satiability. Moreover, brain operations outside of the prefrontal region that have no effect on tolerance for pain also have no effect on satiability.[4]

Method

The measurement of satiability to kinesthetic sensation has been used in this study, adapting the apparatus first described by Köhler and Dinnerstein.[9]

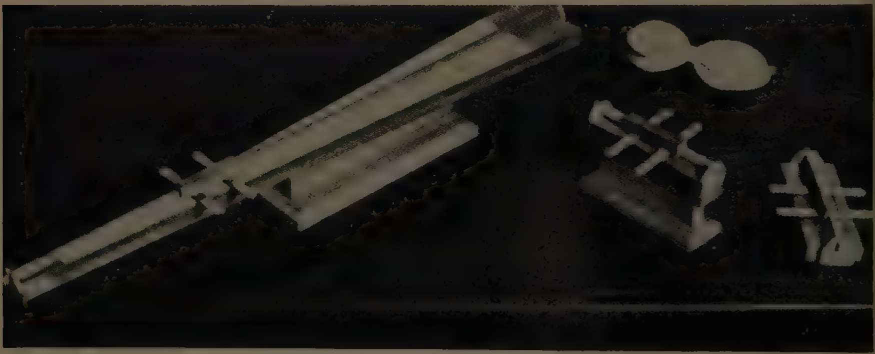

FIGURE 1. Photograph of kinesthetic satiation apparatus.

The subject is occupied for 45 min. answering questions associated with other parts of the investigation and the hands are not used during this period. Such a resting period is essential in order to allow wearing-off of the effect of whatever the subject may have handled prior to testing. Then the subject is blindfolded and feels with his thumb and forefinger of the right hand the width (38.1 mm.) of a test object, a standard block of smooth, unpainted wood. With the thumb and forefinger of his other hand, he feels a long tapered bar of similar unpainted wood and determines the place on the bar where it seems just as wide as the test block (FIGURE 1). Movement back and forth is permitted, and the position of subjective equality for perceived width is thus fixed. The measurement is always made 4 times in succession.

The subject is then given a wider test block (63.5 mm.) to rub with his right-hand finger and thumb at a constant rate for 90 sec. The purpose of this rubbing of a wider block is to induce satiation if it is to occur. After 90 sec. of rubbing, he again equates the original test block to the perceived equivalent width on the tapered bar, determining 4 equivalences.

Next, the satiation rubbing is increased, first to 90 sec. and then to 120, and

4 measurements of the subjective size of the test object are made after each period of satiation. Thereafter, instead of rubbing to induce satiation, an empty interval is allowed to elapse, with measurements of the test object after 15 min.

Reducers and Augmenters

Let us call persons who tend to reduce the size of the block subjectively after stimulation the Reducers, as distinguished from the Augmenters, who tend to enlarge the block.

It had been assumed in previous work that satiability is one process that expresses itself in a change in size, and that the direction of the change is determined by the size of the stimulus object in relation to the size of the test object. We have demonstrated recently, however, that the Reducer will tend to reduce even if he is stimulated for equal amounts of time with a block that is larger than the test object and a block that is smaller than the test object; that is to say, the *total effect* is for him to reduce. The contrary relation holds for the Augmenter who, when stimulated by objects in precisely the same way as the Reducer, will regularly tend to enlarge his estimate of size. What has been demonstrated by our results is that there are here 2 contrasting processes manifesting themselves in different personality types—one, a tendency to enlarge; the other, a tendency to reduce. We have demonstrated this difference in 4 groups—about 46 subjects in all—using various approaches. The particular perceptual style seems to be independent of the relative intensity of the juxtaposed stimuli. As this finding is important theoretically as well as practically and contradicts many implicit assumptions, we must look at some of the figures (FIGURES 2 and 3). These findings are statistically significant beyond the 0.05 level of confidence, and we should bear in mind in all that follows that, given both smaller and larger stimuli, the Augmenter enlarges at least as much as the Reducer reduces.

Our results indicate that the greatest tolerance for pain is shown by the Reducers. These findings suggest that this tolerance for pain is partially due to the subject's tendency to reduce the perceived intensity of stimuli. Thus, an intermittent change in the intensity of a wave of pain may cause later pain to appear less severe.

The difference in the tendency to reduce between those who could and those who could not endure experimental pain* reached the 0.05 level of confidence after only 90 sec. of stimulation (FIGURE 4†). An extreme Reducer diminished the apparent size of the wooden block by 50 per cent after a further 90 sec., and this effect was still partially present 1 hour after all stimulation ceased.

Sensory Deprivation

If the tolerance of the Reducers for pain is partially due to their tendency to diminish the intensity of the stimulation they receive from the environment, then this tendency should become a handicap in a situation where the environment tends to deprive the individual of sensation instead of bombarding him with sensory experience, as in the case with pain. Such sparsity of sensation occurs in the sensory monotony and deprivation accompanying confinement and isolation in chronic illness. The ill effects of acute shortage of sensory input were originally noted by Bexton *et al.*[11] and have since been demonstrated and investigated by a number of other investigators.[12,13] In sensory deprivation, a strong tendency for the Reducer to diminish the perceptual intensity of a sound—after he has heard a louder or softer sound, for example—would make the sum total of sound for him less than that available to the Augmenter. Thus, if this is true, a Reducer would tend to be intolerant of confinement and sensory deprivation, for the limited stimulation would be perceived as less intense.

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* The experimental pain was induced by heat, with the use of an adaptation of the Hardy-Wolff-Goodell dolorimeter.[10]

† Part of the data presented in FIGURES 4 and 5 have been published previously[2] but, being basic, are repeated here.

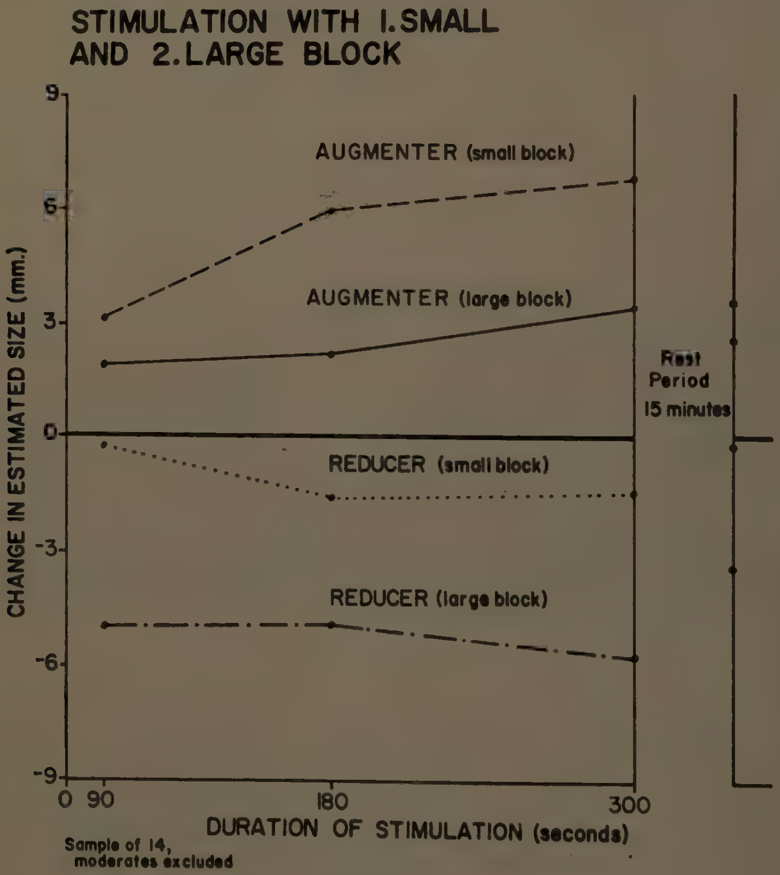

FIGURE 2.

Findings on two different groups of volunteers (17 in all) subjected to sensory deprivation indicate that such is, indeed, the case. These experiments on deprivation were conducted at Boston City Hospital by Wexler *et al.*[14] The findings show that it is the Augmenters who can tolerate starvation of sensation as measured by the number of hours they are willing to remain in a tank-type respirator, whereas it is the Reducers who cannot accept this kind of stress (FIGURE 5). This difference is exactly the reverse of the behavior of these two types under the stress of pain. If the two deprivation groups are treated together, the differences in satiation after 120 sec. of stimulation are significant beyond the 0.01 level of probability.

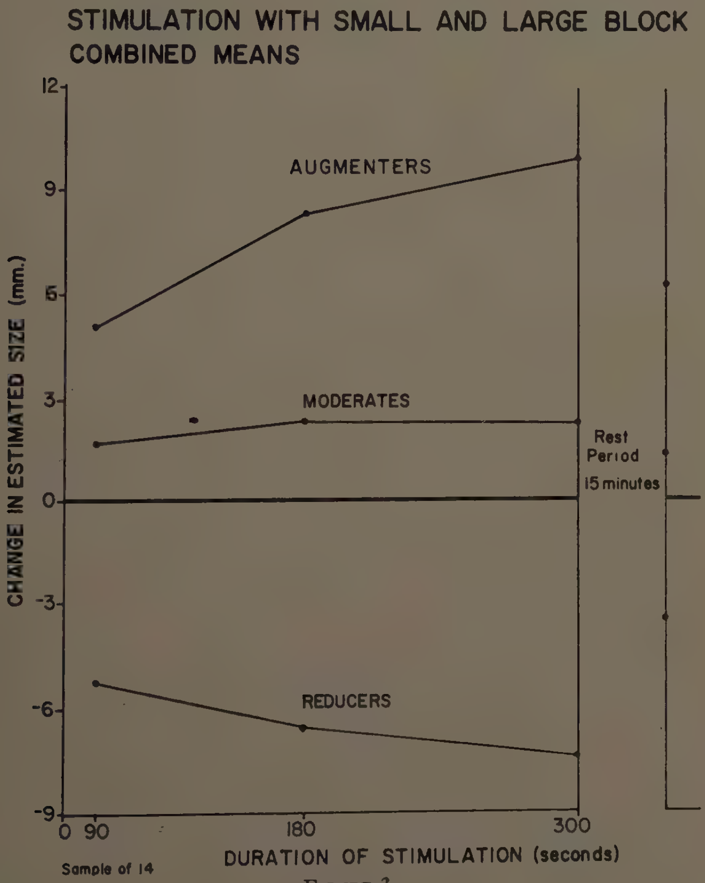

FIGURE 3.

Sex Differences

The third major point concerns sex differences in the subjective reduction of the intensity of sensation. These results are based on the particular population with which we have worked and should be viewed with greater reserve than the other findings.

It seemed possible that there would be a difference in the satiability of adult men and women. The perception of pain in an adult woman protects the new life as well as her own. A woman who is congenitally insensitive to pain, that is to say, who is "pain-blind," does not know when her baby is about to be born nor when it has arrived and needs care; such babies are literally lost. The absence of the experience of pain makes it very difficult for her to behave with tender care toward her vulnerable child. Thus, a woman's perception of pain is inextricably interwoven with the survival of the race, and a tendency of adult females not to reduce sensation much could have survival value. Our results on about 60 subjects indicate some tendency for women to reduce less than men. This difference is shown clearly in FIGURE 6 and reaches the 5 per cent level of confidence. These results on sex differences are supported, moreover, by other findings of Barthol,[15] who used somewhat different techniques on 40 college students.

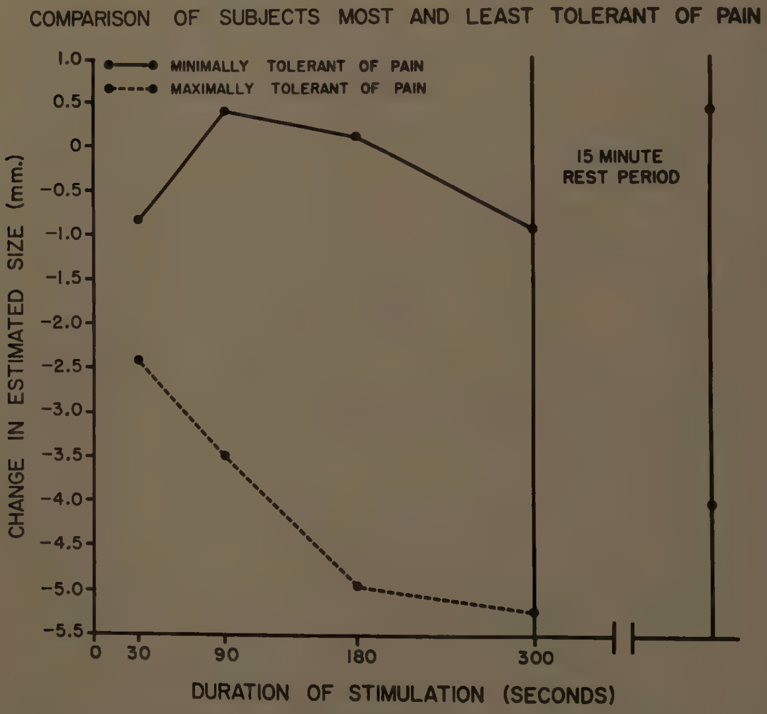

FIGURE 4.

We have not as yet studied the tolerance of confinement in women, but on the basis of their showing a greater tendency to be Augmenters with all the associated characteristics, we predict that (1) women might tend to tolerate confinement better than men and (2) that some of the effects of confinement, such as hallucinations, would be less pronounced in women. A recent announcement of some space research in Canada suggests that this is the case.

If this sex difference is borne out by further research, it would become clear that "men must work and women must weep," not merely because of cultural difference, but also in part because of a difference in basic perceptual styles. It would appear also from our findings that, in addition to the difficulty of one person's ever understanding another, there is, in the case of Reducers and Augmenters, the likelihood that they are seeing, hearing, touching, and feeling all things at different intensities.

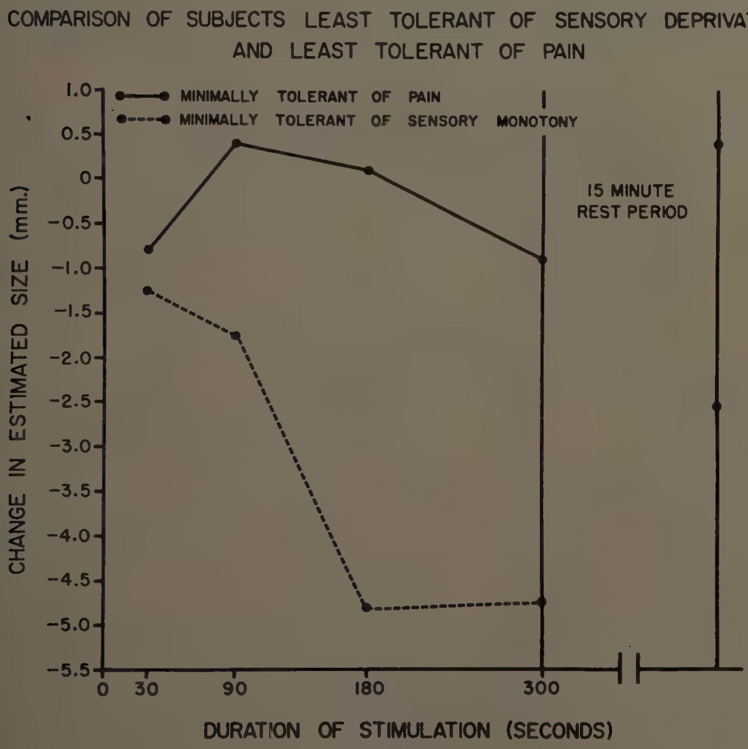

FIGURE 5.

Alcohol

Drugs can achieve a temporary alteration in the tendency to reduce the perceived intensity of stimulation and thus to relieve suffering with pain. One of the first nonopiate drugs used to counteract suffering due to pain was alcohol. In fact, the behavior of some persons after the consumption of alcohol comes to resemble that of a patient after a prefrontal lobotomy. It seemed quite possible that part of the effectiveness of alcohol lies in its causing an increase in the tendency to reduce, at least for some persons. In a pilot study with hospital staff members we have now found that, under the influence of alcohol (even 1 oz. of vodka), such is indeed the case. The most pronounced effect is on the Augmenters who are changed so that they come to resemble the Reducers.

In this experiment, the subjects were volunteers from the staff of Boston Sanatorium. Among them were kitchen and laundry workers, clerks, nurses, surgeons, and physicians. Each was told that he was taking part in an investigation of the effect of alcohol and of alcohol-like drugs. Teetotalers and persons who had had problems with alcohol were excluded. Each subject was seen on three occasions. On the first, nothing was administered, and we obtained a base line from which to estimate the effects of the procedures introduced on the two remaining occasions, the order of which was random. On one of those subsequent occasions, a glass containing grapefruit juice and vodka (80 proof) and a straw were given to the subject by a physician and the subject was instructed to drink it through the straw. On the other occasion, the same procedure was followed with the vodka omitted. On each occasion, the patient was warned not to drive immediately after the experiment and told that other precautions were sensible after the intake of alcohol. Neither the experimenter, nor the subject, nor anyone in contact with them knew whether indeed the patient had been given alcohol or an alcohol-like drug or nothing.

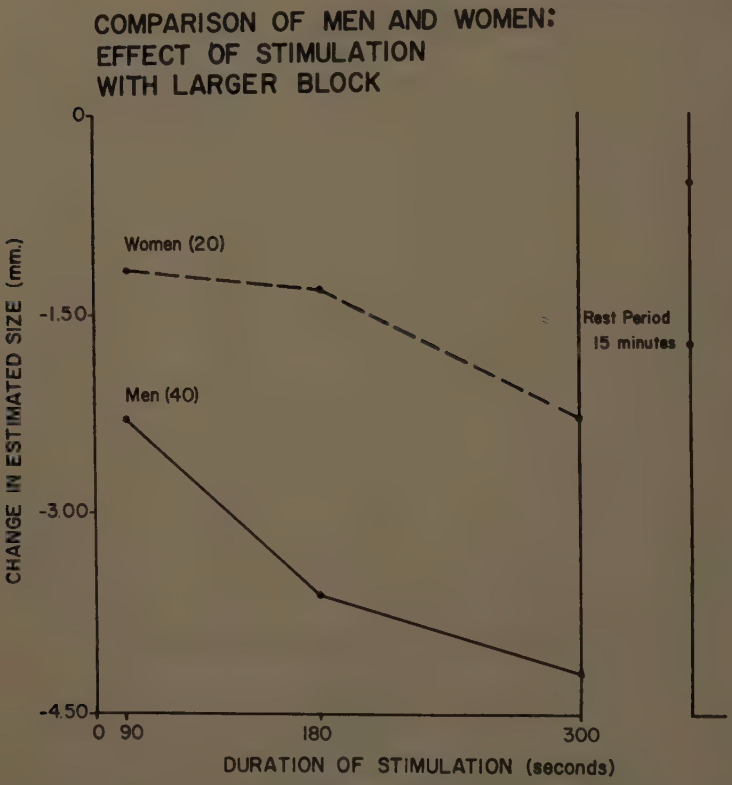

FIGURE 6.

The over-all effect of the alcohol, as compared with the "feigned alcohol," was an increase in the tendency to reduce. Thus, one part of our hypothesis seemed to be supported: the effect of alcohol in increasing the tolerance for pain and suffering could be due partially to its reduction of the sensory intensity.

This over-all view hides, however, the really important findings. If we break down our population into three groups—the Augmenters, the Moderates, and the Reducers—we find that after the consumption of alcohol it is the Augmenters in whom the maximum and dramatic change occurs, for they actually cease enlarging and begin to reduce. This change occurred in every one of our Augmenters. For the average change of the group of Augmenters, p was 0.001. The Moderates, however, showed almost no change at all. The Reducers changed a little, though not to the same extent as the Augmenters, and the direction of their change was to make them reduce less. This is shown clearly in Figure 7 and Table 1.

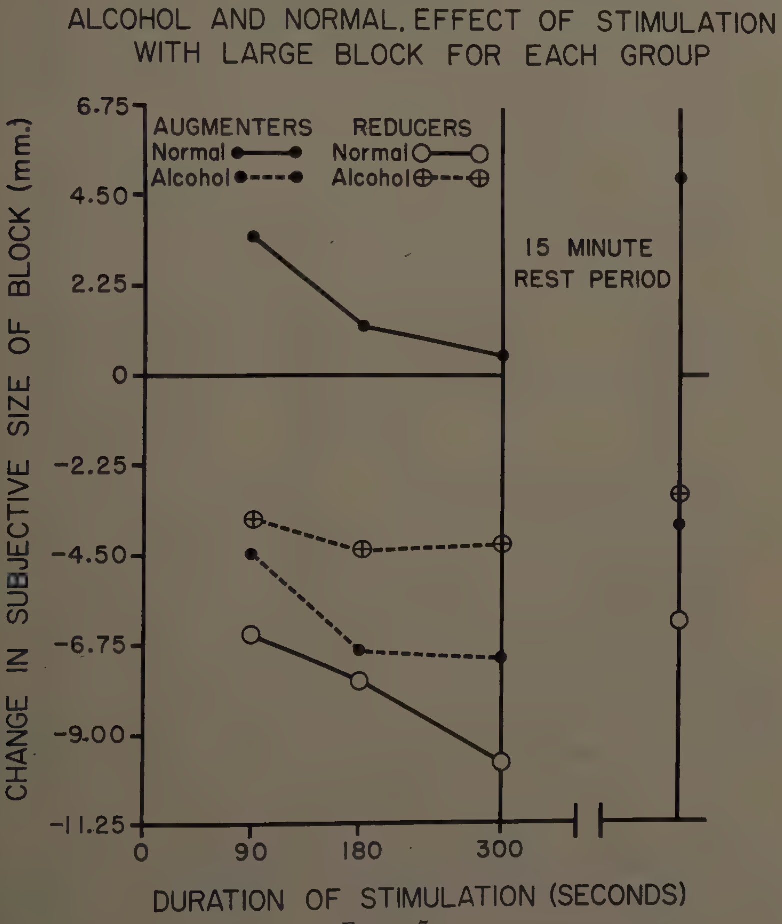

Figure 7.

Analysis of variance was used with these results. The scores obtained after each of the periods of stimulation were compared to ascertain the effect on the normal score of (1) alcohol and (2) the feigned alcohol. The Reducers, Augmenters, and the Moderates were treated separately. In addition to the differences after each period of stimulation, the average effect of the three periods of stimulation was calculated. The bar graph (FIGURE 8) presents the mean effect of the alcohol on the tendency of these three groups to reduce. It will be seen that the effect on the Augmenters is the most pronounced, that there is very little change in the Moderate group, and that the Reducers tend to reduce less than they did. In this connection it is worthy of note that among the alcoholics (the 25 who were contrasted with the 50 nonalcoholics at the Boston Sanatorium) the Augmenters tend to predominate; more often than not the alcoholics are those who suffer more from the insults of the perceptual environment.

A similarity of the effects on the Augmenter of alcohol and of a lobotomy is found in other traits besides his tendency to reduce. The Augmenter's perception of time has changed, and his speed of performance has increased. These time and speed changes, indeed, could have been predicted on the basis of the altered intensity of perception.[2] Moreover, after both alcohol and lobotomy, the Augmenter's endurance of discomfort is increased and his self-criticism and his tendency to blame himself for failure are decreased.

TABLE 1

DIFFERENCE BETWEEN ALCOHOL AND NORMAL SESSIONS IN AVERAGE EFFECT OF STIMULATION WITH LARGE BLOCK*

	Difference in change in estimated size of block (mm.)				
	Duration of stimulation (sec.)			After 15-min. rest	Standard error of difference between means
	90	180	300		
Augmenters, N = 7	−7.92	−8.16	−7.56	−3.78	1.332
Moderates, N = 10	1.92	0.81	0.96	1.11	0.963
Reducers, N = 10	2.91	3.33	5.43	3.18	0.921

* See FIGURE 7.

Feigned Alcohol

Let us pause here to consider the hypothesis under test in the experiment feigning the imbibing of alcohol. If alcohol alters the tendency to reduce, then, in every person whose life history includes the consumption of alcohol, the association between the drug and the alteration has frequently been experienced. Pavlov's dogs, who had frequently experienced increased salivation with the intake of food, were soon found to salivate in response to cues that preceded the intake of food. We now know that such associations of stimulus and response will, in time, not only cause an alteration in smooth-muscle behavior but that, for example, even the EEG pattern can be similarly conditioned.[16] It seemed probable that a consistent association of alcohol with an altered tendency to reduce might come to link this alteration with cues associated with the consumption of alcohol and that, if we could reproduce those cues, we should be able to mimic the effect of alcohol. That is what we were trying to do when we planned our experiment feigning the use of alcohol.

The over-all effect of the feigned use of alcohol is to decrease the tendency to reduce. Actually, the results, when broken down, show that the Augmenter becomes somewhat more of a Reducer, as if he had real alcohol, that the Reducer tends to reduce less, and that the Moderate remains pretty much unchanged (FIGURES 9 and 10; TABLE 2). These findings support the hypothesis hat the change induced by alcohol can be associated with cues that precede he consumption of alcohol; that is to say, we were able in our sample to induce hanges in the tendency to reduce, and we found that the directions of the hanges parallel those achieved with alcohol.

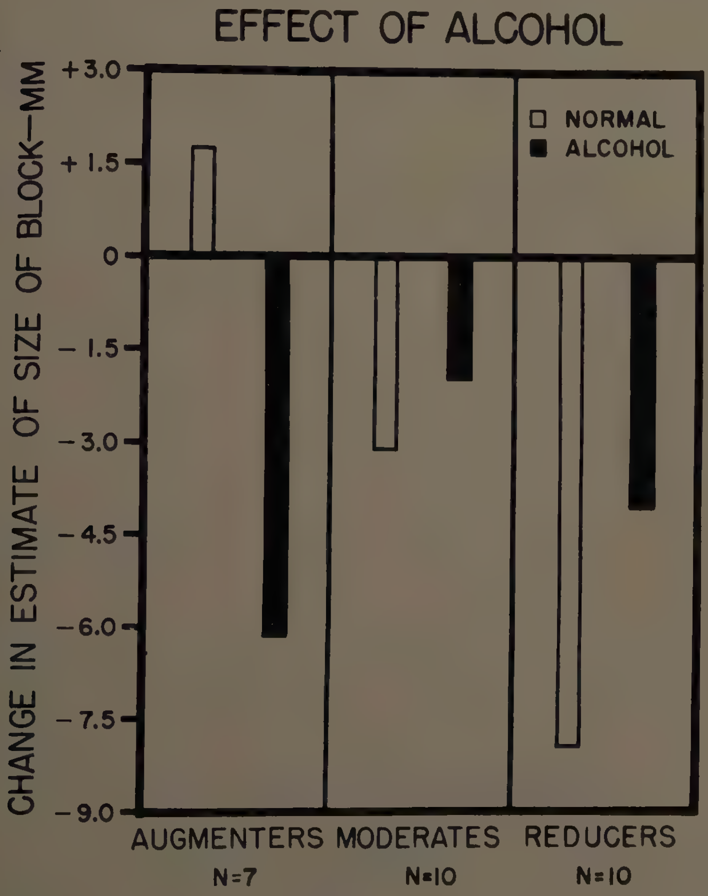

FIGURE 8.

We are now at the beginning of pilot studies with other pain-relieving drugs, nd I suggest that the tendency to reduce may be an important psychological and neurophysiological) effect of other nonopiate drugs that cause increased olerance of pain.

It is in the Augmenter that alcohol causes an alteration in the direction of the change. The change is also maximal in the Augmenter, for he not only ceases to enlarge but now tends to reduce. The Reducer still reduces with alcohol, but less than before. Here is an analogy.

It has been demonstrated that the cochlear nucleus will cease to react to a constantly repeated click of the same sound, but that in a state of drowsiness or deep anesthesia its response may reappear.[17] It may be that the Reducer

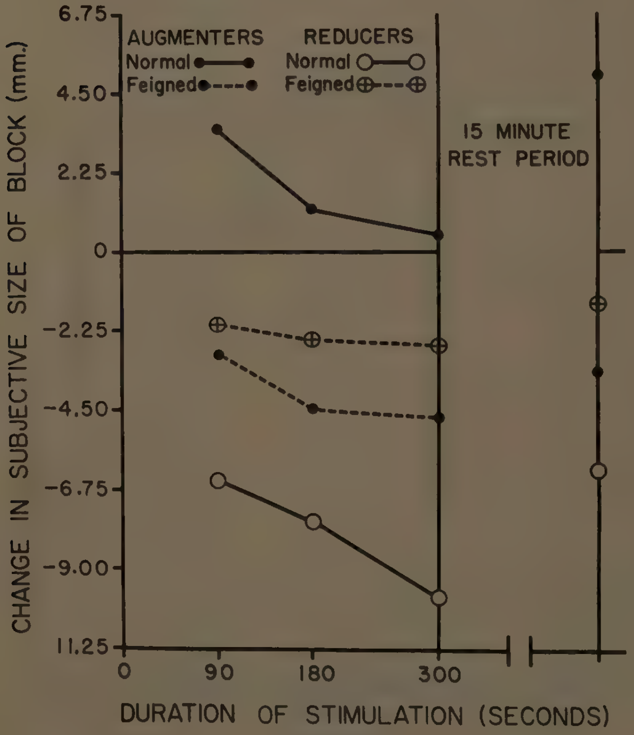
NORMAL AND "FEIGNED ALCOHOL". EFFECT OF STIMULATION WITH LARGE BLOCK FOR EACH GROUP

FIGURE 9.

similarly tends to cease responding fully to habitual stimuli but that, when he imbibes alcohol (equivalent in this analogy to inducing drowsiness), he becomes alerted once more and begins to respond to the habitual stimuli.

If our interpretation of the effects of feigning the administration of alcohol is correct, if it is dependent on previous conditioning, then care must be taken in any attempt to assess the efficacy of a commonly used drug by contrasting it with the effects of a placebo. It seems not improbable that, when the drug has been achieving its intended effect over a period of time, the placebo by association would acquire similar effects, particularly in persons most susceptible to the drug. It would thus be a great mistake to judge a drug as ineffectual

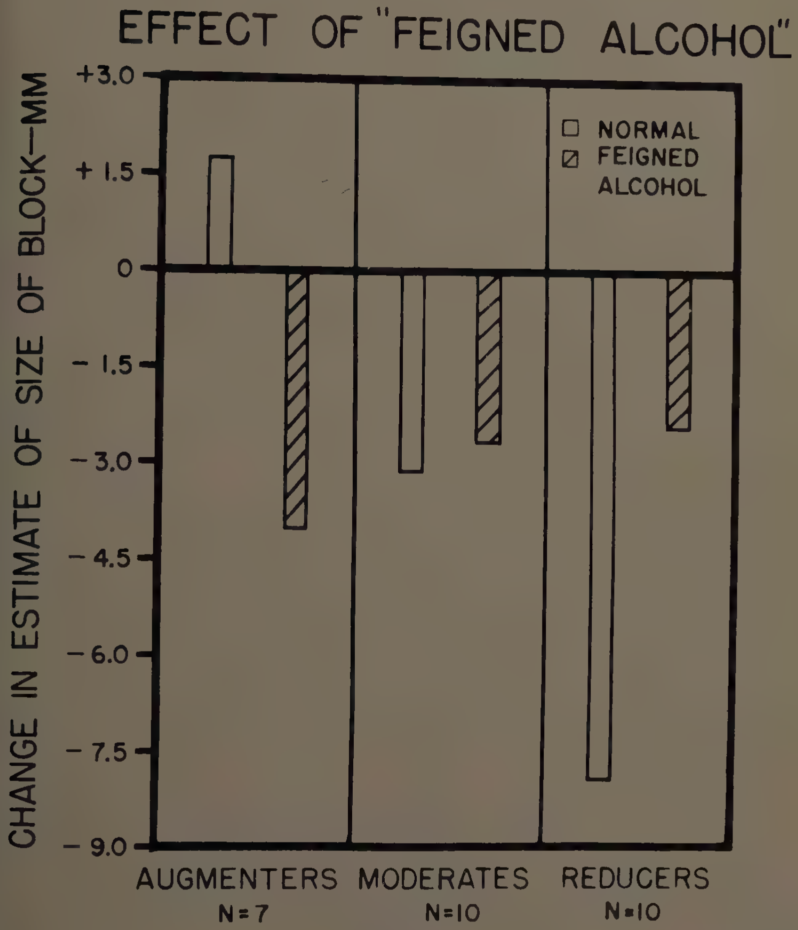

FIGURE 10.

TABLE 2

DIFFERENCE BETWEEN FEIGNED ALCOHOL AND NORMAL SESSIONS IN AVERAGE EFFECT OF STIMULATION WITH A LARGE BLOCK*

	Difference in change in estimated size of block (mm.)				
	Duration of stimulation (sec.)			After 15-min. rest	Standard error of difference between means
	90	180	300		
Augmenters, N = 7	−6.45	−5.73	−5.16	−3.45	1.332
Moderates, N = 10	1.95	−0.69	0.09	−2.01	0.963
Reducers, N = 10	4.35	5.19	7.02	4.68	0.921

* See FIGURE 9.

because these comparable results can be achieved by the so-called suggestion of a placebo.

Pain Tolerance and the Pain Threshold

The tolerance for pain must not be confused with the threshold for pain. Many misunderstandings arise if the two measures are mistakenly identified. This paper considers only tolerance for pain. It undertakes to show that the crucial difference between individuals consists in a difference in tolerance for pain, even though their sensory thresholds may be identical. Thus, a drug that increases tolerance for pain might leave the sensory threshold untouched, as in frontal lobotomy. It would be a mistake to attempt to estimate the effectiveness of a drug on pain by measuring its effect on the threshold for pain instead of on the tolerance for pain.

Summary

The association between tolerance for pain and the tendency to reduce the perceived intensity of a series of juxtaposed stimuli has been outlined in this paper. Moreover, a temporary alteration in the tendency to reduce can be achieved with alcohol and possibly with other nonopiate drugs that relieve pain. It appears that the most pronounced effect of alcohol occurs in those who tend to intensify experience, changing them so that they now show a strong tendency to reduce; there are pronounced differences in the effects of alcohol on this particular variable, differences that depend on the perceptual style of the individual. An increase in the tendency to reduce may, indeed, be one of the most important psychological (and neurophysiological) effects of the nonopiate drugs that cause increased tolerance for pain.

Acknowledgments

This work was done at Boston Sanatorium and Beth Israel Hospital, Boston, and with the collaboration of Boston City Hospital. I acknowledge the irreplaceable aid of Walter Collins and Roberta Cohen in the current work, and am also grateful to Betsy Abrams, Christine Chase, and Annette Silbert for assisting with the testing of patients and subjects, and to Ulric Neisser,[18] who carried out all the testing in the experimental pain study. Suzanne Bailey and Joan Kennedy helped in numerous ways. The work has benefited by statistical advice and assistance with regard to some of the data from M. C. Sheps and Rita Nickerson of the Department of Preventive Medicine, Harvard Medical School. E. G. Boring, of Harvard University, has helped immeasurably as consultant on this project.

References

1. Petrie, A., W. Collins & P. Solomon. 1958. Pain sensitivity, sensory deprivation, and susceptibility to satiation. Science. **128:** 1431–1433.
2. Petrie, A., W. Collins & P. Solomon. 1960. The tolerance for pain and for sensory deprivation. Am. J. Psychol. **73.** In press.
3. Petrie, A. 1952. Personality and the Frontal Lobes : 86–99. Blakiston. New York.
4. Petrie, A. 1958. Effects of chlorpromazine and of brain lesions on personality. *In* Psychopharmacology. : 99–115. H. D. Pennes, Ed. Harper. New York.
5. Köhler, W. & H. Wallach. 1944. Figural after-effects. Proc. Am. Phil. Soc. **88:** 269–357.

6. Wertheimer, M. 1955. Figural after-effect as a measure of metabolic efficiency. J. Personality. **24:** 56–73.
7. Klein, G. S. & D. Krech. 1952. Cortical conductivity in the brain injured. J. Personality. **21:** 118–148.
8. Eysenck, H. J. 1957. The Dynamics of Anxiety and Hysteria. : 31. Routledge & Kegan Paul. London.
9. Köhler, W. & D. Dinnerstein. 1947. Figural after-effects in kinesthesis. *In* Miscellanea Psychologica A. Michotte. : 196–220. Louvain ed.
10. Hardy, J. D., H. G. Wolff & H. Goodell. 1952. Pain Sensations and Reactions. : 67. Williams & Wilkins. Baltimore.
11. Bexton, W. H., W. Heron & T. H. Scott. 1954. Effects of decreased variation in the sensory environment. Can. J. Psychol. **8:** 70–76.
12. Lilly, J. C. 1956. Mental effects of reduction of ordinary levels of physical stimuli on intact healthy persons. Psychiat. Research Repts. **5:** 1–28.
13. Solomon, P., P. H. Leiderman, J. H. Mendelson & D. Wexler. 1957. Sensory deprivation, a review. Am. J. Psychiat. **114:** 357–363.
14. Wexler, D., J. Mendelson, P. H. Leiderman & P. Solomon. 1958. Sensory deprivation: a technique for studying psychiatric aspects of stress. A.M.A. Arch. Neurol. Psychiat. **79:** 225–233.
15. Barthol, R. P. 1958. Individual and sex differences in cortical conductivity. J. Personality. **26**(3): 365–378.
16. Gastant, H., A. Jus, C. Jus, F. Morrell, W. S. Van-Leeuwen, S. Dongier, R. Naguet, H. Regis, A. Roger, D. Bekkering, A. Kamp & J. Werre. 1957. Étude topographique des réactions électro-encéphalographiques conditions chez l'homme; essai d'interprétation neurophysiologique. Electroencephalog. and Clinical Neurophysiol. **9:** 1–34.
17. Hernandez-Peon, R. &. R. Hagbarth. 1955. Interaction between afferent and cortically induced reticular responses. J. Neurophysiol. **18:** 44–55.
18. Neisser, U. 1959. Temperature thresholds for cutaneous pain. J. Appl. Physiol. **14:** 368–372.

THE CLINICAL MEASUREMENT OF PAIN

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Although pain is difficult to define and its quality almost impossible to describe, its presence and severity can be measured with relative ease in a variety of clinical states. The quantification of clinical pain—by which I mean pain occurring spontaneously as a symptom in patients, as opposed to pain produced in the laboratory for experimental purposes—has as its basic tenet the postulate that the simplest and most reliable index of pain is the patient's verbal report. The use of concomitants of pain (palmar sweating and resistance, or alterations in pulse rate) and the use of observers—"people-watchers"—who try to assess a patient's distress solely by external nonverbal clues, such as facial expressions, are not particularly useful because of the poor correlation of such data with pain. The investigator who would study pain is at the mercy of the patient, upon whose ability and willingness to communicate he is dependent. Fortunately, most patients are both willing and able to cooperate with the clinical investigator in the measurement of pain.

A wide variety of techniques has been employed to assess the efficacy of analgesic compounds. It is impossible to compare the relative efficacy of most of these techniques in discriminating between active and inactive drugs because direct comparisons of the different methods have been attempted only rarely. It is, however, possible to choose between techniques on theoretical grounds or because one technique will provide certain kinds of data whereas another will not.

In general, it would appear desirable to use graded rather than quantal data in measuring pain, since it is usually possible by so doing to squeeze more out of one's data and improve the efficiency of experiments. The quantal (or "yes-or-no") approach is exemplified by the reporting of the incidence of pain relief after the administration of a given drug to a group of patients. The apparent simplicity of this technique is deceptive. What is to be defined as pain relief? Complete absence of pain is the least equivocal end point, but hardly the only one. Another end point is the achievement of significant relief, which can be variously defined, as for example the disappearance of most of the pain or of more than half the pain. Another possibility is to give credit for *any* degree of pain relief, be it slight or complete.

But also, what of the temporal aspect of such pain relief? Must the end point chosen be reached within a maximal period of time (such as 1 hour) to be counted as a success? Must it last a minimal period of time, such as 1 or 2 hours? Or will pain relief at any time after drug administration be considered a successful trial? The preference in our own laboratory for the presentation of such quantal data is shown in FIGURE 1. Here complete relief from pain, a clear-cut end point that is easily comprehended by both patient and reader, is used as the dependent variable, and the data are presented by plotting against time the percentage of patients claiming complete relief from pain at various intervals after administration of drug.

Graded measurement may utilize some such scheme as the following: the patient is asked to categorize his pain initially as slight, moderate, severe, or very severe. Drug is then administered and the patient is asked to categorize his pain again at various intervals thereafter. To permit mathematical treatment of pain relief, a scoring system is needed. The simplest technique is to consider each step from one pain level to the next as a unit of one, so that a drop in pain severity from very severe to severe, severe to moderate, moderate to slight, or slight to none achieves a "pain-relief score" of 1; a drop from very severe to moderate, or moderate to none, a score of 2. (Obviously the same sort of temporal aspect is included in such evaluation as was described previously for quantal data.) Some results with this type of scale are shown in FIGURE 2.

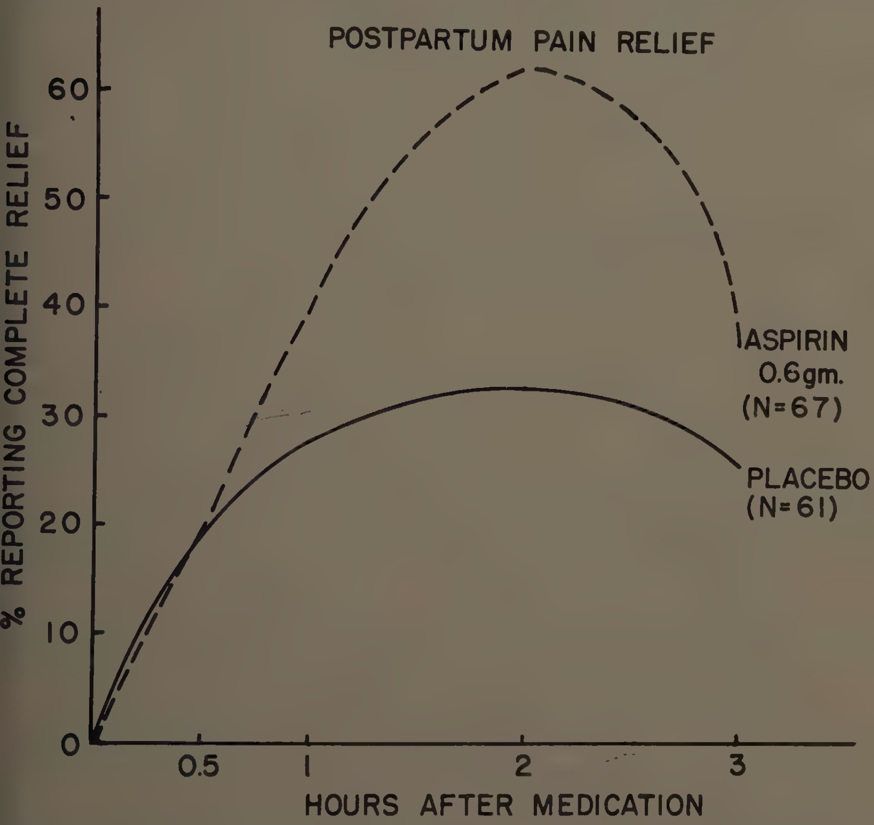

FIGURE 1. Per cent of patients reporting complete relief of postpartum pain at various intervals after administration of medication.

Is the equal-step approach just described a legitimate one? There are several ways of answering this question. One is to see whether this equality of decrements corresponds to reality; that is, whether patients feel equally grateful for decreases in pain from any one level to the next. We have tried to get at this point in two ways. The first was to present a "pain thermometer" to subjects, asking them to place at appropriate "temperatures" the pain points very severe, severe, moderate, and slight. By then calculating the number of degrees between pain levels it was hoped that one would have some measure of the relative importance assigned to these levels by different people.

Another method was to request that subjects rank, in order of importance to them, four theoretical analgesic results: a change in pain from very severe to severe, severe to moderate, moderate to slight, and slight to none. The question used was: "For which of these changes in pain intensity would you be most grateful, least grateful," and so forth until all four situations had been ranked.

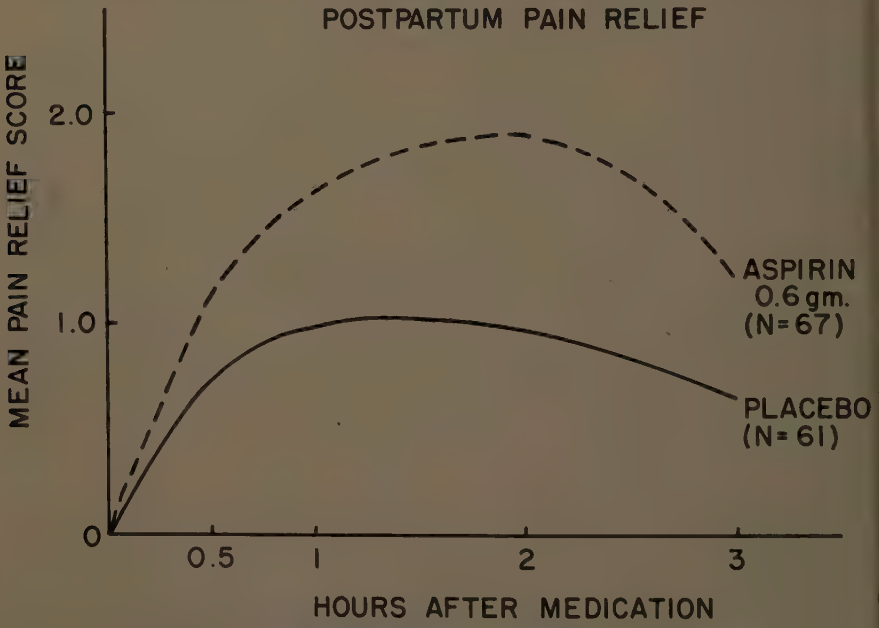

FIGURE 2. Mean pain relief scores in study of postpartum pain.

The results of these investigations suggested that a drop of pain from severe to moderate was, on the average, considered most important, and a drop from slight to none least important. There was, however, amazing variability in responses, with every possible ranking being displayed and, most important, the differences in pain decrements were not of great magnitude (see TABLES 1 and 2).

Still another technique for investigating the validity of the equal-step approach is that known as discriminant function analysis. Here the question might be: "What intervals in such a pain scale serve most efficiently to separate active from inactive drugs?" In this case also, we have failed to come up with any weighting of pain scores which serves to increase significantly the yield over that supplied by the simplest (that is, the equal-step) approach. Houde and his colleagues at Memorial Hospital in New York City have tried various manipulations of their own data and have similarly failed to come up with a useful transformation.

I will now take up briefly a number of other points regarding the recording of analgesic performance.

(1) The use of global performance scores incorporating efficacy and toxicity data, such as has been recommended by some, can be justified on clinical grounds, since useful analgesics must be both potent and nontoxic; however, reports of trials that contain only such data are both confusing and misleading. For one thing, investigators (and patients) may differ considerably as to the price they are willing to pay for pain relief, so that one investigator's standards may not apply to any other laboratory. Second, a global score which confers points for analgesia and subtracts points for toxicity may, in the end, equate a potent but toxic drug with a safe but inactive agent. It may be quite important, for example, to know that nalorphine is a potent analgesic, even if its side effects preclude its use in the clinic.

TABLE 1

"PAIN THERMOMETER" DATA (MEAN "DEGREES" OF PAIN BETWEEN PAIN LEVELS)

	Very severe to severe	Severe to moderate	Moderate to slight	Slight to none
Nonpatients* (43)	22	31	26	17
Negro patients (35 females)	23	25	26	24
White patients (29 females)	21	28	22	23

* Male and female physicians, technicians, secretaries, and students.

TABLE 2

RANKING OF DECREMENTS OF PAIN INTENSITY (MEANS)*

	Very severe to severe	Severe to moderate	Moderate to slight	Slight to none
Nonpatients† (43)	2.6	3.3	2.2	1.7
Negro patients (35 females)	2.0	3.3	2.4	2.0
White patients (29 females)	2.7	3.2	2.6	1.5

* On a scale from 4 (decrement of pain intensity considered most impressive) to 1 (decrement of pain intensity considered least impressive).

† Male and female physicians, technicians, secretaries, and students.

(2) In certain clinical situations, such as the postoperative period, attempts o interview patients will be handicapped at times by the fact that patients will be asleep. One then has the choice of waking such patients for a few minutes or interview, or of assuming that since the patient is asleep he has no pain. Unfortunately, if one wakes up such patients, one is amazed to find that the ssumption of "no pain if asleep" is a faulty one (see TABLE 3). Theoretically, t least, an analgesic with a strong sedative effect might look better than an qually analgesic but nonsedative drug, if all sleeping patients were assumed to be free of pain. The data from wakened patients can be analyzed in two ways, hat is, by equating sleep with complete analgesia and by using the actual subective reports elicited after awakening.

(3) There has been a certain amount of controversy over whether it is best to have patients make absolute statements, such as "my pain is now moderately bad," or relative statements, such as "my pain is much less than before I received the injection." The second approach obviously requires that a patient remember what the original pain was like, and that he not confuse the original interview point with subsequent postdrug interviews. The first approach also requires a comparison, however, in that a patient presumably judges the pain at the moment of interview by an "internal standard" of various degrees of pain, based on the individual's past algesic experiences. (It would seem, for example, that a person who had never previously experienced pain would be in a poor position to categorize his first painful experience as slight, moderate, or severe.) In actual practice I believe both techniques work well in acute experiments with intelligent patients, although one might hazard the guess that the longer the interval between drug administration and the eliciting of pain relief the greater the risk that will be involved in a system relying on the patient's memory of what the original pain was like.

(4) The duration of pain relief is best estimated by repeated interviews at, let us say, hourly intervals, but here one must often compromise between what one would like to have in the way of data and the practicalities of the situation. In our laboratory we employ routinely, with inpatients, hourly interviews for 4 to 6 hours after drug administration; we do not believe that much information is lost by limiting the period of observation to this length of time. Although trials have been reported in which duration of effect and, indeed, efficacy itself have been estimated from the interval between a patient's requests for medication, such techniques involve assumptions that are always risky. Such estimates are better than no estimates, however, and may be justified on occasion by the simplicity of the device.

TABLE 3

VERBAL REPORTS OF PAIN IN 45 POSTOPERATIVE PATIENTS AWAKENED FOR INTERVIEW AFTER DRUG ADMINISTRATION

No pain	31%
Slight pain	45%
Moderate pain	22%
Very severe pain	2%

The use of very infrequent interview points, such as weekly assessments by outpatients who are on chronic drug administration, deserves some comment at this point. Our experience suggests that such assessments are subject to gross distortions because of the mnemonic problems involved. If one engages in this type of study, it is best to have patients fill out reports on postcards and mail them off to the investigator each day so as to diminish the strain on memory and improve the quality of the data.

(5) The principle of "crossover," "patient-as-his-own-control" studies has, regrettably, achieved the status of a fetish among many investigators. It is quite true that patients differ from each other in many ways and that there are occasions when the repeated use of a subject may increase the precision of the data. It is equally true that few patients receiving drug repeatedly return

to exactly the same baseline before each treatment, and that the repeated dosing of a patient with medications also raises the specters of tolerance, carryover effects, and so forth. The availability of limited clinical material may argue in favor of the repeated use of the same patients, but it does not remove from the investigator the need to examine his data for evidence of difficulties imposed by his technique. In our studies with postoperative pain, we usually alternate two medications over a 36- to 48-hour period. We attempt to analyze for the effects of the order of administration by comparing the results obtained with all doses with the results obtained with first doses only, where each patient contributes data only on the first dose he received (FIGURES 3 and 4). Thus far we have not been impressed with order effects, but obviously the possibility of such always exists.

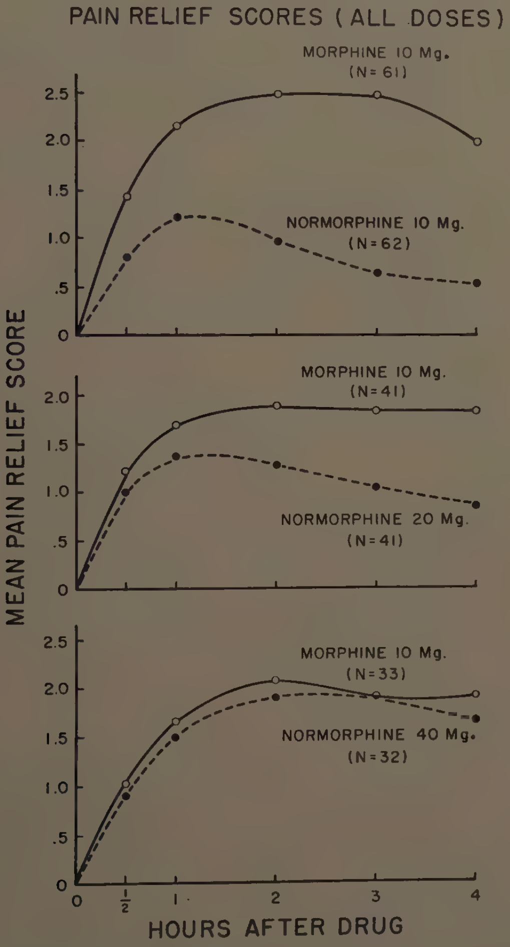

FIGURE 3. Mean pain relief scores in three trials comparing normorphine and morphine in postoperative patients (all doses administered).

Indeed, in at least one study on postpartum pain, drug-order interactions reported were of such magnitude that an inactive medication given second to a patient looked better than an active drug given first. The authors in question marshalled convincing evidence that in their system, at least, crossover designs were inefficient. A doctrinaire approach to this problem is unquestionably a dangerous one.

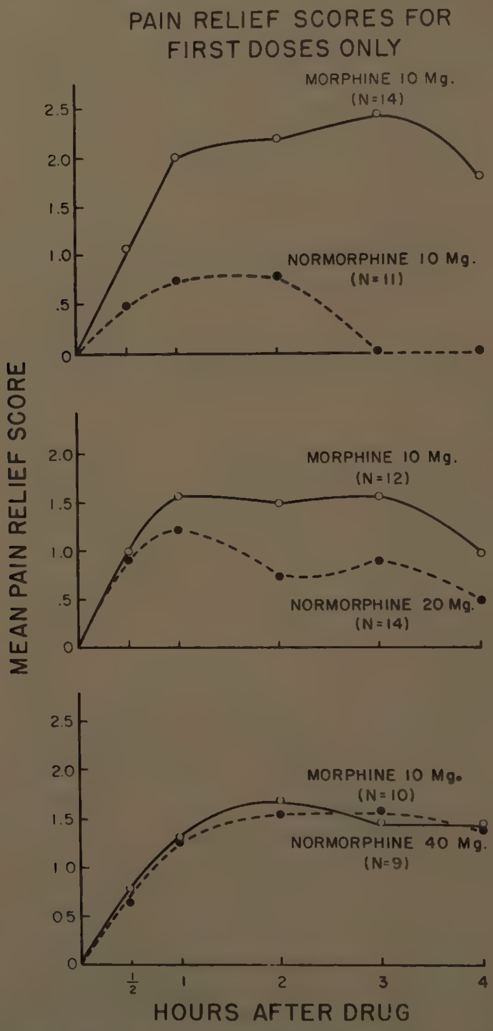

FIGURE 4. Mean pain relief scores in three trials comparing normorphine and morphine in postoperative patients (first doses only).

When patients are repeatedly exposed to a given drug, and different patients receive different numbers of doses, another statistical problem arises. Most of us are really interested in how a number of *patients* respond to a drug, not in how a number of *doses* perform. If one patient receives fifty doses of drug whereas most patients receive one or two doses, the one atypical patient may unduly bias the data if each dose is counted equally. On the other hand, one ought to have more confidence in the data when repeated observations are made than when only one dose has been studied. There would seem to be a need for

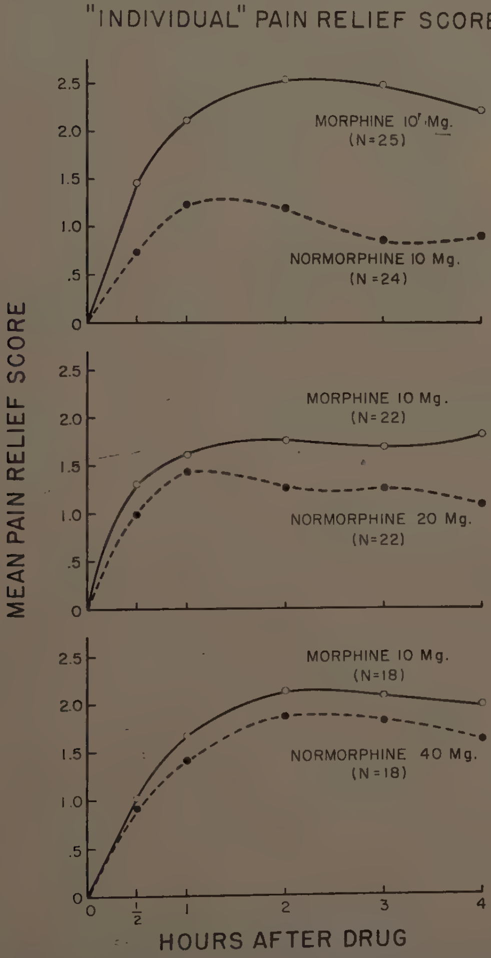

FIGURE 5. Mean pain relief scores in three trials comparing normorphine and morphine in postoperative patients ("individual" scores).

statistical techniques for weighting responses and improving the efficiency of analysis. Our own present incomplete solution in such situations is to calculate individual mean scores per patient: regardless of how many doses of a drug the patient has received, the data are averaged and a mean score for that patient given that drug is calculated. Then these individual scores for all patients are averaged and a grand mean score for that drug calculated, with each patient contributing equally (FIGURE 5). This begs the question a bit, but it is preferable, we believe, to mean scores based on a straight averaging of all doses.

(6) The type of pain studied deserves some comment. It is obvious that a clinical trial requires a supply of patients of some kind. But availability is not synonymous with quality, and investigators would do well occasionally to question whether their particular system contains defects which affect the precision of their data and the ease of generalizing from that particular situation to other clinical states. Theoretically, at least, there is the possibility that a drug useful for relieving postpartum pain may not help cancer pain or headache. Certainly a sedative effect is desirable in some pain situations and undesirable in others. In point of fact, however, there is a paucity of evidence to document the opinion that analgesics are differentially useful in various pain situations. Aspirin, for example, is a valuable pain reliever in pain states as different as headache, postoperative pain, postpartum pain, and pain of malignancy.

(7) I have said nothing about the need for controls, perhaps because this general aspect of clinical trials has been covered many times before. The importance of random allocation of treatments, the use of placebos or standard drugs as anchoring points, should need no emphasis, yet I will be surprised if several reports given in this monograph do not neglect these basic and sensible principles, with the result that our curiosity will be titillated but our scientific souls left unsatisfied, beset by doubts and suspicions. I am well aware of the lack of precedence for adequately controlled trials in some of the very therapeutic areas with which we are most concerned in this monograph, but this is a poor reason *not* to conduct proper trials.

In conclusion, the evaluation of analgesic agents is now on a satisfactory basis in that the techniques have been well worked out, in large part, in theory and practice. A new drug alleged to have pain-relieving properties deserves to be studied under controlled conditions in a variety of types of pain. Without controls, reports on analgesic efficacy amount to little more than testimonials. Without trials in different clinical situations, one cannot tell whether an agent is generally useful (or useless) across the board as a pain reliever or effective (or ineffective) only in certain kinds of painful states. Pitting the new drug against a standard drug such as morphine or aspirin is essential to the proper pigeonholing of a new agent. It is one thing to say that a drug has *some* analgesic effect; it is quite another to say that it is an improvement over previously available agents.

No single negative or positive report on a new drug—no matter how well controlled the experiment—should be accepted as the final word on the efficacy or potency of a drug. On the other hand, it is unlikely that a truly effective drug will be missed by several investigators in properly controlled trials of respectable size, or that an agent found to be efficacious in several such trials will later prove to be a dud. Nevertheless, there are so many variables that need study regarding a new drug—dose, route of administration, single versus repeated dosage, and so on—that I find it difficult to visualize a time when we will be able to escape the considerable amount of effort presently required in working up a new analgesic.

In reporting analgesic trials, I would plead for more detailed presentation of data on the types of patients studied and particularly on the criteria used and the details of recorded response. It is often difficult to analyze reports in the literature because of scantiness of the detail supplied. (One recent report even went to the extreme of failing to supply the code for two of the medications used in the study.)

Finally, I believe that it is important to give the negative side of the generally optimistic picture I have presented. What one cannot tell from the literature is the frequency with which well-designed trials fail to discriminate between drugs that differ in efficacy or fail to produce respectable dose-response curves. Unpublished data in various laboratories can testify to the occurrence of this phenomenon. What is even more disturbing, occasionally a laboratory will find an agent to be significantly better than another in one trial only to have the position of the drugs reversed in the next trial. For the most part it is impossible to do more than guess at the factors which might account for these perplexing results. The point is that caution, critique, and restraint are constantly needed in evaluating reports and that while analgesic testing in patients—the ultimate criterion of success, overshadowing all experimental studies in animals or healthy men—is not as difficult as some skeptics would believe, it is also harder than some enthusiasts would propose.

THE PHARMACOLOGY OF SALICYLATES AND RELATED COMPOUNDS*

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Since the salicylates are among the oldest remedies that still occupy an important place in modern therapeutics, and since they have been used more widely and in larger quantity than any other medicinal agent, it is appropriate to consider their pharmacological properties before discussing drugs that are just now being introduced for similar therapeutic uses.

A comprehensive bibliography of the earlier literature is that of Gross and Greenberg (1948), and more recent reviews have been prepared by P. K. Smith (1949) and M. J. H. Smith (1953). Some of the material also is included in a recent textbook (P. K. Smith, 1958).

This discussion will be limited to some of the more recent work on the salicylates and related drugs. No attempt will be made to include or refer to all of the voluminous literature on these drugs. Since acetylsalicylic acid and sodium salicylate are the compounds most frequently used, most of the discussion will be concerned with these. Other related compounds are discussed separately toward the end of the presentation.

Effects on the Central Nervous System

Antipyresis. The salicylates in moderate doses have no effect on normal body temperature and influence only the patient with fever, returning body temperature toward or to normal by increasing heat elimination. Their principal action seems to be through a dilation of the small vessels of the skin. The action is nonspecific in that it is not related to the reduction of the infection or other underlying cause. Salicylates may act as antipyretics primarily by increasing heat dissipation through the mobilization of water and consequent dilution of the blood. The action promotes perspiration, which in turn causes cutaneous dilation. All these actions probably are mediated centrally.

Pyresis. Whereas salicylates in moderate doses have long been known to be valuable as antipyretic agents there is now considerable evidence that they increase metabolism and oxygen consumption and that toxic doses may induce fever. While other factors such as dehydration undoubtedly contribute, children suffering from salicylate intoxication frequently have very high body temperatures (Segar and Holliday, 1958). The general effects on metabolism will be discussed later.

Analgesia. At least four methods are in use for measuring the degree of effectiveness of salicylates and other analgesic agents: (1) testing the effects of the agent upon the reaction of an animal to noxious stimulation; (2) measuring the rise in pain threshold of normal human subjects; (3) measuring the pain-reducing effects on normal human subjects with experimentally induced pain;

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and (4) measuring the pain-reducing effects in patients experiencing pain spontaneously. While animal testing serves as a rough assay of analgesia and tests on normal human subjects may yield a more precise assay of potency, measurements in patients with pain define the effectiveness of these agents under circumstances most relevant to suffering.

Beecher (1957) refers to many ingenious methods for pain production in man, such as pricks of the skin, tourniquets on the arm, heat, and electric shocks to the teeth. In his opinion they are without usefulness in man; appraisal of real analgesic power must be based upon the capacity of the agent to relieve natural pain present as a consequence of disease or trauma, inasmuch as the pain experience of man consists of perception of painful stimuli together with the psychic modification of these stimuli.

That experimentally induced pain is not the same as that observed clinically cannot be proved or disproved readily. However, in terms of the interpretation of pain impulses, differences may be out of all proportion to the intensity of the stimulus. Suggestion is a potent factor, modifying discrimination of pain threshold following administration of analgesic agents in experiments attempting measurement of analgesic action. For example, a subject who knows he is being given an analgesic will demonstrate more elevation of the pain threshold than will a subject who is receiving the same agent, but is convinced that he has not received an analgesic drug.

In a well-controlled experiment with postsurgical patients, Beecher *et al.* (1953) reported that 0.6 gm. of aspirin given orally was more effective as an analgesic than 10 mg. of morphine or 60 mg. of codeine given orally. Others have confirmed this. Gruber *et al.* (1956) found that doses of 325 mg. acetylsalicylic acid were approximately equivalent to doses of 32 mg. codeine phosphate in patients with chronic pain. Good relief was obtained by Orkin *et al.* (1957) in 30 per cent of patients with postobstetrical pain given placebos, in 44 per cent given 0.6 gm. aspirin, in 50 per cent given 30 mg. codeine, in 36 per cent given 0.5 gm. *N*-acetyl-*p*-aminophenol, and in 35 per cent given 4-aminoantipyrine.

Usually it has been assumed that analgesic drugs act at the site to which ascending painful stimuli are communicated. Analogy suggests that the antipyretic and analgesic actions occur approximately in the same area, and this has led to the assumption that analgesia resides in the hypothalamic nuclei.

Others attempt to explain the action of certain analgesic drugs such as the salicylates solely through their effect on the water balance of tissues. Myalgia is known to occur when metabolic products accumulate in muscle more rapidly than they can be carried away. The resultant edema is a conspicuous concomitant of this event and is frequently grossly apparent in sore muscles. Arthralgias are frequently associated with inflammation and edema. In view of these observations it has been postulated that salicylates reduce pain by reducing the edema associated with pain. Thus, instead of acting on the symptoms of the pain, they may well remove or alleviate the cause of the pain.

Aspirin seems to have a specific effect on inflamed tissue that causes a reduction in edema in these tissues where other substances that may act on normal tissues will fail. For instance, edema produced in the hind paws of rats by the injection of serotonin will be inhibited by the subcutaneous administration of 600 mg. sodium salicylate per kg. (Kelemen, 1957). Similarly, when swelling is produced in the hind legs of rats by the injection of formalin, aspirin depresses the swelling in normal but not in adrenalectomized rats (Bacchus and Bacchus, 1953). Randle and Selitto (1957) have devised a method for measuring analgesic activity in rats by producing inflammation in the foot by a yeast injection and measuring the increased pressure on the foot required to produce struggling after an effective analgesic drug has been given. Under these circumstances aspirin has an analgesic effect.

Respiration. The average analgesic dose of acetylsalicylic acid (0.3 gm.) does not affect respiration. However, respiration is increased in both rate and depth after large doses of salicylates, as the result of a direct central stimulating action of the drug. In most cases of salicylate intoxication respiration is deep and rapid, and the rate may be as high as 38/min. First, there is a primary hyperventilation due to central stimulation, and later a ketosis develops, with a bicarbonate-deficit type of acidosis. Probably the ketosis is not related directly to the administration of salicylate, since it occurs after voluntary hyperventilation and may result from the administration of alkali.

In normal human subjects 12 gm. of aspirin given over a period of 8 hours produces a respiratory alkalosis with an average increase in respiratory volume of 4 l./min. (Farber *et al.*, 1949). There is frequently an alkalosis with a rise in blood *p*H, together with numbness and tingling of the extremities similar to that occurring in tetany. Severe dyspnea occurs in patients with an average plasma-salicylate level of 35 to 50 mg. per cent. Salicylates may cause an increase in the depth of respiration and a marked and progressive increase in oxygen consumption of normal human subjects (Cochran, 1952). Tenney and Miller (1955) showed that, in dogs, sodium salicylate has a direct respiratory stimulant action. The locus of the effect is in the medulla and is independent of aortic and carotid chemoreceptor areas.

Other central effects. Several other effects of the salicylates on the central nervous system are well known. The effects in their milder form are so common in patients receiving large doses that the term salicylism is applied to them. In advanced intoxication other symptoms may occur, including delirium, stupor, and coma. Seizures have been observed after toxic doses in rats (Whitehead and Woodbury, 1958); these do not occur early but later, in the acidosis phase, and may be due to carbon dioxide accumulation.

Moderate doses of aspirin (250 mg./kg.) do not prolong pentobarbital hypnosis in rats as do certain other analgesic drugs (Eckhardt *et al.*, 1958).

Effects on the Gastrointestinal Tract

In rheumatic-fever patients in whom high plasma levels of salicylate are maintained, nausea is common as a side effect, but nausea is almost as frequent after intravenous as after oral administration of the drug. Nausea has been reported to occur at salicylate-plasma levels of about 37 mg. per cent regardless of whether the drug is given orally or intravenously. However, some workers find that the vomiting is not necessarily related to the plasma levels. Graham and Parker (1948) report that, although vomiting occurs at an average plasma-salicylate concentration of 28 mg. per cent, in children with rheumatic fever, vomiting is not necessarily related to the blood-salicylate level and therefore may result from a local effect of the drug on the gastrointestinal tract.

Gastrointestinal irritation may occur after large doses of salicylates. In some cases of intoxication the gastrointestinal tract shows hemorrhage and alteration, but in other cases signs of gastrointestinal alterations are absent. Muir and Cossar (1955) observed that in patients with peptic ulcers, aspirin was a gastric irritant and that it played a significant part in the exacerbation of ulcer symptoms. Kelley (1956) observed a group of patients who gave evidence of gastrointestinal hemorrhage after the ingestion of salicylates. Bleeding was painless, free acid was found in the fasting stomach, and no roentgenographic proof of an ulcer was present. Aspirin ingestion always preceded the bleeding. The prothrombin concentrations were normal in all cases examined. Salicylates were incriminated in many of the peptic ulcer patients observed by Alvarez and Summerskill (1958). Both soluble and insoluble aspirin were related to occult-blood loss in the stools. Habitually heavy consumption of salicylate compounds coincided with the onset and subsequent course of anemia in 2 patients who had been under iron treatment for years. After salicylate consumption was greatly reduced the anemia did not recur (Summerskill and Alvarez, 1958). Occult loss of blood was observed in about 70 per cent of 140 rheumatic patients and 40 healthy persons given aspirin as tablets or powder, 1.5 to 3.0 gm. per day (Stubbé, 1958).

It is not possible at this time to evaluate properly the possible role of the salicylates in the production of gastric irritation. Whether the effects are due to local irritation from relatively insoluble acetylsalicylic acid and may be avoided by giving the drug as a more soluble preparation cannot now be concluded. Alvarez and Summerskill found no less irritation with soluble preparations of aspirin, but Stubbé observed a lower incidence of occult blood loss in patients given enteric coated tablets of sodium salicylate. Others (Matsumoto and Grossman, 1959) labeled human erythrocytes with radiochromium and found that the average fecal excretion of radioactivity was greater in patients who had ingested 3 gm. aspirin per day for 3 or 6 days. Although an alkaline solution of aspirin produced the same effect as aspirin tablets, in no instance could bleeding under these experimental conditions be classified as clinically important gastrointestinal hemorrhage.

Another possible factor in gastric irritation is that observed by Smith (1954*a*), who found that intraperitoneal or intravenous injection of salicylate in rats delayed the passage of a barium meal from the stomach, which normally requires less than 2 hours, to 12 hours or more. A sodium chloride solution was without effect (Smith and Irving, 1955). This observation raises the possibility that patients already under salicylate therapy may retain the drug longer in the stomach, which increases the chances of irritation.

Effects on the Cardiovascular System

The effects of the salicylates on the cardiovascular system are limited to vasodilatation, discussed under the heading of antipyresis, since the action occurs through the central nervous system. Therapeutic dosages of the salicylates are not known to have any deleterious effects on the heart. Large doses, up to those causing salicylism, produce no effects upon the normal human electrocardiogram. Sodium salicylate, in doses of 100 mg./kg. injected intravenously into dogs, produces a consistent but moderate and brief increase in heart contractile force (Walton and Darby, 1958). Intravenous doses in dogs increase the right ventricular pressure and the cardiac output by a direct stimulating effect on cardiac muscle (Tenney and Miller, 1955). Salicylate is a specific antagonist of the constrictor action of serotonin on the blood vessels of the forearm and hand. This may be due to the secondary release of, or synergism with, some other substance, perhaps a hormone (Glover *et al.*, 1957).

Sodium salicylate in a concentration of 5 mM causes a marked stimulation of oxidative metabolism of the isolated toad heart, and pretreatment with salicylate abolishes the inotropic response to ouabain or lanatoside-C (Nayler, 1957).

Immunological Phenomena

Because of the favorable action of salicylates in rheumatic fever, many investigators have been concerned with possible effects of salicylates on immunological reactions. Oral administration of salicylates decreases the incidence of death from anaphylactic shock produced in rabbits by the injection of egg albumin (Lepper *et al.*, 1950). The mechanism of action is not antihistaminic, nor does it appear to be related to characteristic pharmacological effects, such as antipyresis. Sodium salicylate decreases the severity of the coronary lesions induced by the injection of bovine gamma globulin fraction II in rabbits (Moore *et al.*, 1952). Salicylates, as well as cortisone, inhibit the phenomenon of local tissue reactivity in rabbits (Shwartzman and Schneierson, 1953). Also, the joint swelling in the Arthus reaction in the guinea pig can be suppressed by sodium salicylate or cortisone (Coburn and Haninger, 1954). Aspirin may have afforded some protection to mice sensitized to gamma globulin (Cameron, 1957). Using a typical antiprotein and a typical antipolysaccharide antigen-antibody system, Friend (1953) observed that sodium salicylate, aspirin, *o*-methoxybenzoic acid, *m*-hydroxybenzoic acid, and *p*-hydroxybenzoic acid inhibited the characteristic precipitation. In this system, the usual salicylates are not unique in their effect.

When salicylates are given, the C-reactive protein disappears from the plasma of rheumatic fever patients (Hill, 1952). Aspirin, ACTH, and cortisone all cause decreases in the titer of antistreptolysin "O" in patients, but smaller effects were obtained with aspirin. Similar effects on gamma globulin concentration were also observed (Stolzer *et al.*, 1954).

It may be concluded that salicylates exhibit some protective effect against anaphylactic shock and may act in some way to prevent the combination of antigen and antibody, but it remains to elucidate the mechanism of this phenomenon.

Effects on Acid-Base Balance

Acid-base balance changes and disturbances in electrolyte pattern probably are related to respiratory stimulation. Singer (1954) analyzed the blood from patients with salicylate intoxication and concluded that the acid-base disturbance was initially a primary respiratory alkalosis due to direct stimulation by the drug. Later a primary metabolic acidosis occasionally developed, the cause of which was not known. In almost every case measured, the carbon-dioxide combining power was reduced and the carbon-dioxide dissociation curve was of the hypocapnic type, owing either to the production of acid or to respiratory stimulation. Evidence that the diminished carbon-dioxide capacity and rise in *p*H are due to respiratory stimulation with a subsequent loss of carbon dioxide has been presented by several investigators. Normal subjects receiving 12 gm. of aspirin exhibited an average rise of 0.06 in blood *p*H and a fall in plasma bicarbonate of 3 millimoles per liter (Farber *et al.*, 1949).

Effects on the Adrenal Gland

Clinical findings resembling Cushing's syndrome in a patient under salicylate therapy prompted Hetzel and Hine (1951) to study the effect of salicylate on the ascorbic acid content of the adrenal glands of rats. The effect was proportional to the dose. The response was abolished by hypophysectomy (Cauwenberge, 1951) and inhibited by preliminary treatment with cortical hormones. Little *et al.* (1954) also found that salicylate produced a significant depletion of adrenal ascorbic acid in the rat, as was confirmed by Feeney *et al.* (1955). Lesions of the median eminence of rats completely blocked adrenal ascorbic depletion by 150 mg./kg. aspirin (George and Way, 1957).

Sodium salicylate or sodium acetylsalicylate induced thymus atrophy in immature or adrenalectomized rats. The effects of salicylate and hydrocortisone were additive (Stephenson, 1958).

In rare instances, rheumatic fever patients have exhibited some of the clinical features associated with adrenal hypersecretion. The effects were rounding of the facial contours, acne, diminished glucose tolerance, glycosuria, and alteration of the mental state (Cochran *et al.*, 1950). Some have pointed out that one feature of Cushing's syndrome, puffiness of the face, may be observed in almost every patient receiving full therapeutic doses of salicylate, and it tends to be more pronounced in children. These observations have led to numerous attempts to delineate the role of the adrenals and pituitary in the action of salicylates.

In guinea pigs sodium salicylate increased the concentration of 17-hydroxycorticosteroids in the plasma. This effect did not take place if the guinea pigs were hypophysectomized or adrenalectomized (Good *et al.*, 1957).

Normal adult human subjects given no more than therapeutic doses of salicylates did not show consistent increases in plasma concentrations of 17-hydroxycorticosteroids. Sometimes there was even a reduction (Done *et al.*, 1955*a*). However, patients with salicylate intoxication had high blood levels of 17-hydroxycorticosteroids. This was not a general stress reaction, since the elevation was less marked in patients severely ill from other causes (Done *et al.*, 1954). In contrast to nonrheumatics, patients with active rheumatic fever did not develop elevated-plasma 17-hydroxycorticosteroid concentrations in response to salicylate intoxication, perhaps because the adrenals of rheumatic fever patients are relatively refractory to stress (Done *et al.*, 1955*b*).

Smith *et al.* (1954*a*, *b*) observed that salicylates did not cause an increased excretion of adrenal steroids in rheumatic fever patients, and they rejected the hypothesis that salicylates exert their therapeutic activity in rheumatic diseases by stimulating the anterior lobe of the pituitary and the adrenal cortex. Ely *et al.* (1955) observed that the urinary excretion of 17-hydroxycorticosteroids in patients with rheumatic fever was no less than in normal subjects prior to salicylate administration.

No significant increase in the concentration of circulating adrenal cortical hormones was observed by Bayliss and Steinbeck (1954) in patients under prolonged treatment with acetylsalicylic acid or in patients receiving single 3.3-gm. doses of sodium salicylate. This has been confirmed by others (Done *et al.*, 1958). Rheumatic fever patients, whether treated with salicylates or bed rest alone, did not differ significantly in their plasma concentrations of 17-hydroxycorticosteroids (Seely *et al.*, 1955). Prolonged therapy resulted in a period of posttherapy adrenal unresponsiveness similar to the effect produced by cortisone (Done *et al.*, 1958). Aspirin produced an acute decrease of approximately 40 per cent in the concentration of plasma corticoids in patients with rheumatoid arthritis. It also diminished the response to corticotrophin (Herndon *et al.*, 1958).

These observations may not be inconsistent. It has been suggested that salicylates may both stimulate the pituitary and accelerate the removal of corticosteroids from the plasma by means other than urinary excretion (Done *et al.*, 1958).

Effects on Metabolism

Quite recently, M. Smith (1959) published an excellent, more extensive review of the effects of salicylates on metabolism.

Oxygen consumption. In carefully controlled experiments with human subjects, Cochran (1952) showed that either orally or intravenously administered salicylate caused a marked increase in oxygen consumption. The observed fall in respiratory quotient suggested that protein and/or fat were being metabolized predominantly. In each subject studied the respiratory quotient showed a progressive fall during salicylate therapy and reached its lowest level at about the time of maximal oxygen consumption. Tenney and Miller (1955) observed that in dogs, salicylate was a profound metabolic stimulant and sometimes doubled the oxygen consumption. The maximal effect was produced by intravenous doses of 100 mg./kg. The increase was due primarily to the effect on skeletal muscle; it was independent of the nervous system. In rats, a decrease was observed in CO_2 and O_2 tensions due to increased alveolar ventilation and relatively greater increase of tissue O_2 consumption (Miller and Tenney, 1956).

Fishgold *et al.* (1951) found that sodium salicylate increased the oxygen consumption of slices of rat cerebral cortex, but that sodium acetylsalicylate was without effect. Anaerobic glycolysis of brain tissue was not affected by salicylate. Liver-slice oxygen consumption was not changed by sodium salicylate, but it was increased by sodium acetylsalicylate. The respiration of rat brain homogenates in the presence of glucose or glutamate was markedly stimulated by 0.015 *M* salicylate, but not by *m*- or *p*-hydroxybenzoic acid (Patel and Heim, 1954). With 10 to 40 mg. sodium salicylate per 100 ml. medium, the oxygen consumption of normal human leukocytes increased in proportion to the drug concentration. At higher concentrations oxygen consumption was reduced (Bisset and Alexander, 1958).

Sodium salicylate in a concentration of 5 mM caused a marked stimulation of oxidative metabolism of the isolated toad heart. Pretreatment with salicylate or dinitrophenol abolished the inotropic response to ouabain or lanatoside-C (Nayler, 1957).

There is further evidence for direct effects of salicylates on the metabolism of animals and patients. Doses of 400 mg. sodium salicylate per kg. in dogs consistently produced a hyperpyrexia with circulatory features similar to those described for dinitrophenol (Walton and Darby, 1958). Children suffering from salicylate intoxication frequently have very high body temperatures (Segar and Holliday, 1958).

The basal metabolic rate of 4 myxedematous patients was restored to normal level with aspirin in daily doses of about 8 gm., which also shortened the circulation time and lowered the serum cholesterol (Alexander and Johnson, 1956). When Hetzel *et al.* (1959) gave single oral doses of 5 gm. sodium salicylate to human volunteers, there was a 40 per cent increase in oxygen consumption and a significant decrease in plasma cholesterol. Sodium *p*-hydroxybenzoate produced no effect.

Oxidative phosphorylation. Low concentrations of salicylate stimulate the oxygen consumption of slices of mouse liver, and salicylate resembles dinitrophenol in this respect. Brody (1956) has observed that salicylates uncouple oxidative phosphorylation in liver, kidney, and brain mitochondria. Also, they inhibit fatty acid oxidation by rat-liver mitochondria. Like dinitrophenol, they enhance the liberation of inorganic phosphate from adenosine triphosphate. They depress oxidative phosphorylation and also increase the oxygen consumption of liver and muscle slices. Others have confirmed that salicylate may inhibit the synthesis of high-energy phosphate bonds (Smith and Jeffrey, 1956*a*). *In vitro*, the salicylates inhibit brain glycolysis and uncouple oxidative phosphorylation from oxygen uptake during the oxidation of pyruvate by tissue homogenates and the mitochondria of brain tissue (Penniall *et al.*, 1956).

Doses of 250 or 500 mg. of salicylate per kg. inhibited the incorporation of acetate into liver glycogen by interfering with the production of energy-rich phosphate bonds (Smith, 1958*b*). Penniall (1958) observed that salicylate uncoupled phosphorylation from the oxidation of β-hydroxybutyrate, glutamate, and ferrous cytochrome *c* of rat-liver mitochondria at concentrations of 10^{-4} M. In an acceptor-free system it stimulated oxygen uptake and acetoacetate formation from β-hydroxybutyrate. Salicylate affected mitochondrial swelling in hypotonic media and other processes in a manner similar to that of other uncoupling agents such as dinitrophenol.

Under aerobic conditions the uptake of glucose by the rat diaphragm was increased by 0.25 millimole of 2:4 dinitrophenol or 5 millimoles sodium salicylate, but not by 5 millimoles *p*-hydroxybenzoate (Randle and Smith, 1958*a*). The uptake of glucose was increased still further by adding insulin. These effects occurred in a bicarbonate medium, but not in a phosphate medium.

Both sodium salicylate and dinitrophenol limited the growth of wheat coleoptiles in proportion to the concentration of drug (Reid, 1957).

Salicylate interfered with the normal respiratory processes of the small intestine of rats, and hence with the energy supply necessary for active transport of glucose and fluid (Smith, 1958*a*). The loss of potassium from isolated rat diaphragm was much greater under the influence of oxygen lack or in the presence of sodium salicylate (Randle and Smith, 1958*a*).

Nitrogen metabolism. A progressive rise in urinary nitrogen due to increased protein catabolism and a respiratory alkalosis with a marked reduction in cellular water has been observed by Reid *et al.* (1950). Doses of 160 mg. of aspirin per day to rats cause an increase in nitrogen excretion at a time when suppression of glycosuria is maximal (Ingle and Meeks, 1952). Children with rheumatic fever have a much greater negative nitrogen balance when given cortisone than when given salicylates (Albanese *et al.*, 1954).

Carbohydrate metabolism. The salicylates have profound effects upon carbohydrate metabolism. Aspirin given subcutaneously to depancreatized male rats suppresses the glycosuria proportional to the dose of drug (Ingle and Meeks, 1952). Salicylate reduces the glycosuria and hyperglycemia induced by cortisone in the normal rat. Liver glycogen is depleted and the deposition of new glycogen is prevented under the influence of cortisone (Smith, 1952*a*). Salicylate reduces the glycosuria and blood glucose in alloxan-diabetic rats, but causes no change in the content of liver glycogen (Bornstein *et al.*, 1952). In the normal rat, salicylate depresses the liver glycogen, but does not change the blood glucose (Smith *et al.*, 1952).

Ingle *et al.* (1953) gave aspirin to normal and adrenalectomized rats and found that, when the drug was stopped, there was a temporary exacerbation of the glycosuria to much higher levels than were noted during the preinjection period. The responses in both groups of animals were so similar that they concluded that the effect was not mediated by the adrenal glands. Ingle gave aspirin to partially pancreatized male rats and found that the glycosuria was suppressed in proportion to the dose. The failure to cause exacerbation of the diabetic state suggested that aspirin does not cause a state of hypercorticalism (Ingle, 1953). Sproull (1954*a*) gave mice 10 mg. of sodium salicylate intraperitoneally and observed that the liver glycogen decreased in one to two hours irrespective of sex, or whether the animals were fed or fasted immediately before the experiment. There was hyperglycemia in the females, but not in the males (Sproull, 1954*b*).

Smith fed rats for 1 hour each day and then injected them with salicylate. Initially, there was a decrease in liver glycogen and a decrease in blood glucose, but after 24 hours the concentrations were higher than in the control animals. In adrenalectomized rats the initial effects were similar, but there was no recovery after 24 hours (Smith, 1954*b*). Later the same investigator found that the injection of salicylate caused a considerable delay in the gastric emptying of a barium meal, increasing the emptying time from less than 2 hours to 12 hours or more. He concluded that this was the cause of the liver glycogen depletion previously observed (Smith, 1954*a*).

Rats treated with salicylate absorbed glucose more rapidly than control animals. The presence of the adrenals was essential for this effect (Smith, 1954*c*). When Smith (1955*a*) gave 500 mg. of sodium salicylate per kg. intraperitoneally to rats he observed hyperglycemia at 1, 2, and 3 hours. There was less hyperglycemia in adrenal-demedullated rats, but hypoglycemia in adrenalectomized rats was marked. Fasting rats given large doses of sodium salicylate failed to deposit liver glycogen even when they were given hydrocortisone, yet they continued to have a negative nitrogen balance (Winters and Morrill, 1955). Hypophysectomy did not prevent the depletion of liver glycogen by aspirin and sodium salicylate (Feeney *et al.*, 1955).

When the rat diaphragm was incubated anaerobically or in the presence of salicylate or of insulin, added glucose did not accumulate in the cells, presumably being converted to muscle glycogen (Randle and Smith, 1958*b*). Salicylate caused an increased glycogen breakdown and lactic acid accumulation under both aerobic and anaerobic conditions in the isolated rat diaphragm (Smith, 1955*b*). It also caused an increased oxygen uptake and respiratory quotient and a decreased glucose uptake (Smith and Jeffrey, 1956*b*).

Salicylate, like insulin, increases the uptake of glucose by muscle and enables D-xylose to enter muscle cells. Unlike insulin, it promotes a loss of muscle potassium. Presumably, the effects are due to inhibition of production of energy-rich phosphate (Manchester *et al.*, 1958). When diabetic patients were given 5 to 8 gm. of aspirin per day for 2 weeks, the glycosuria was abolished and the blood sugar was lowered with clinical improvement (Reid *et al.*, 1957). More recently Hecht and Goldner (1959) gave diabetic and nondiabetic patients 4 to 8 gm. aspirin per day for 1 to 3 weeks and observed a moderate though significant hypoglycemic effect in most instances. The drug had an insulin-sparing effect, and appeared to enhance the action of tolbutamide. There was no evidence that it altered glucose absorption, renal excretion of glucose, insulin sensitivity, or hepatic glycogenolysis.

Uric acid. Salicylates lower the renal threshold for uric acid. In patients with chronic gout, the maximum fall in serum uric acid occurs a few days after the administration of salicylate begins, but the fall is not maintained (Marson, 1954). Single doses of 6.5 gm. sodium salicylate have approximately double the uricosuric effect of single doses of 2 gm. probenecid during the 6 hours following administration of the drugs. In normal human subjects, moderate single doses of salicylic acid or acetylsalicylic acid more than double the excretion of uric acid. There is a transient rise in plasma uric acid suggesting that there is an increased production of uric acid, since there also is a more rapid excretion (Crone and Lassen, 1955*a*). Since doses of 2 gm. of salicylate increase the excretion of uric acid without changing the glomerular filtration rate, the drug probably lowers tubular reabsorption of urate (Crone and Lassen, 1955*b*). In rabbits, doses of 50 mg. of salicylic acid per kg. do not alter the ratio of uric acid clearance to creatinine clearance if the plasma concentrations of uric acid are within normal limits, but it reduces the uric acid clearance if the uric acid concentration of the plasma is raised. Poulsen (1955) also concluded that salicylate inhibited the tubular transportation of uric acid.

Enzymes. In *in vitro* experiments sodium salicylate inhibits the uptake of radioactive sulfur in cartilage, whereas related compounds do not (Boström and Månsson, 1955). It is postulated that this inhibition of sulfate exchange with chondroitin sulfuric acid may be related to the antirheumatic activity of the substance.

Kaplan *et al.* (1954) found that α-ketoglutaric dehydrogenase and succinic dehydrogenase are markedly inhibited by salicylate. Inhibition of the former was reversed by magnesium ions. In rheumatic fever, administration of aspirin is associated with an increase in the serum concentrations of glutamic oxaloacetic and glutamic pyruvic transaminases (Manso *et al.*, 1956). Sodium salicylate and sodium acetylsalicylate inhibit the synthesis of glutamine by guinea pig brain at concentrations that stimulate oxygen consumption. There is no inhibition in a cell-free system (Messer, 1958).

The *in vitro* synthesis of salicyluric acid from salicylic acid and glycine occurs with slices of rat liver and kidney and rabbit liver, but not with dog liver and kidney slices. Salicylic acid inhibited the synthesis of *p*-aminohippuric acid in all tissues studied (Little *et al.*, 1957).

Absorption and Distribution

Absorption of the free acid, salts, and esters of salicylates occurs readily after cutaneous application. Absorption of sodium salicylate from the oral cavities is relatively slow. Careful studies in man have shown that when aspirin is placed in the mouth absorption is negligible if the patients are warned not to swallow their saliva. In such experiments complete recovery of aspirin was obtained from the saliva and mouth washings.

More than one half of small doses of salicylic acid were absorbed in one hour from the rat stomach. The rate was almost twice as rapid as for acetylsalicylate. The drugs in a solution of sodium bicarbonate were absorbed much less rapidly. This was explained as due to the reduction, with increasing *p*H, of the proportion of un-ionized acid (Schanker *et al.*, 1957).

In human subjects, the rate of absorption depends to an appreciable extent on the time taken to empty the stomach. Effervescent mixtures containing salicylate decrease this time, owing partly to the weak alkalinity of the solution and partly to the carbon dioxide produced (Carló *et al.*, 1955).

Similar results were obtained in normal subjects. There was relatively rapid absorption of acetylsalicylate and even more rapid absorption of salicylate (Hogben *et al.*, 1957). Atropinized subjects in the left supine position had significant early blood concentrations largely due to absorption directly from the stomach (Truitt and Morgan, 1958).

The absorption of salicylate and acetylsalicylate in the small intestine is related to the degree of ionization of the acids. Schanker *et al.* (1958*a*) attribute this to the fact that the drug crosses the intestinal barrier by diffusing through a boundary which is selectively permeable to the un-ionized form. The rate of absorption of salicylate by the small intestine is reduced severalfold as the acidity of the solution is reduced from *p*H 4 to *p*H 8. The rate of absorption of acetylsalicylate also is reduced as the *p*H of the fluid is increased (Hogben *et al.*, 1959). It is interesting that salicylic acid is absorbed more rapidly in humans than acetylsalicylic acid, a weaker acid (Levitt, Davison, and Smith, unpublished data).

When salicylate was given to rats with experimental fever, absorption was more rapid than in nonfevered rats (Crabtree *et al.*, 1956).

In contrast to the rapid absorption from the upper gastrointestinal tract, salicylates are absorbed rather slowly when given rectally, although measurable concentrations may be detected in the urine 15 min. after administration. After 2 hours the plasma concentrations of salicylate were comparable in normal subjects given 0.6 gm. aspirin either by rectal suppository or orally (Cacchillo and Hassler, 1954). Schanker *et al.* (1958*a*) investigated the absorption of salicylate from the large intestine of the rat and found it less well absorbed than weaker acids.

Concentrations of salicylate in plasma are a more precise measure of the amount of the drug in the body than are the concentrations in whole blood, since the concentrations in the erythrocytes and in plasma are not the same (Parker, 1948). After a single oral dose of 2 gm. of sodium salicylate in normal young men, the average peak salicylate level in the plasma is approximately 15 mg. per cent and is reached in 100 to 120 min.

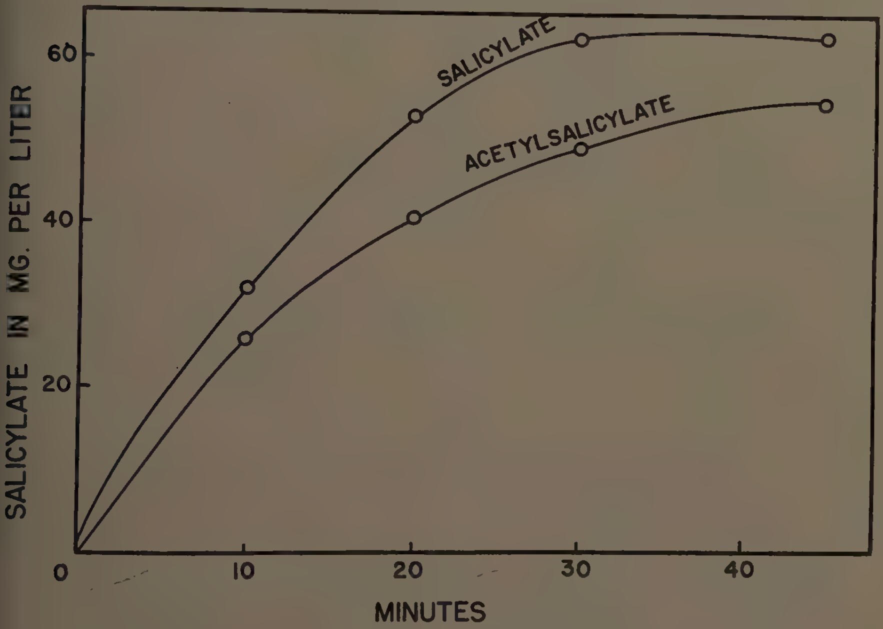

FIGURE 1. Concentration of salicylate in plasma after administration of salicylate and acetylsalicylate to human subjects.

Plasma salicylate concentrations after the administration of choline salicylate to human subjects indicated quite rapid absorption (Broh-Kahn, 1959). The initial plasma concentrations of salicylate were appreciably higher after the administration of choline salicylate than after the administration of an equivalent amount of acetylsalicylic acid (Wolf and Aboody, 1959). When acetylsalicylate and salicylate salts of the same metal are compared, the plasma concentrations of salicylate are appreciably higher initially than those of acetylsalicylate (FIGURE 1).

The salicylates are distributed through a volume of body water much greater than that of the extracellular fluid. Studies on rats showed that the concentrations in the liver, kidney, and lung were similar to those in the serum (Smith *et al.*, 1946). When the salicylate concentration is calculated on the basis of water content, the liver contains about two thirds as much as the serum, muscle approximately one fifth as much, the kidneys one third to one half as much, and the lungs one half to two thirds as much. The concentration of salicylates in the erythrocytes of normal subjects and rheumatic fever patients during treatment is quite low and of the same order of magnitude as would be expected if the concentration in the red cells were similar to that found in the plasma ultrafiltrate.

When sodium salicylate is given to rats, the concentrations of salicylate in the brain are much less than in the plasma. Even after 12 to 24 hours there is more in the plasma (FIGURE 2).

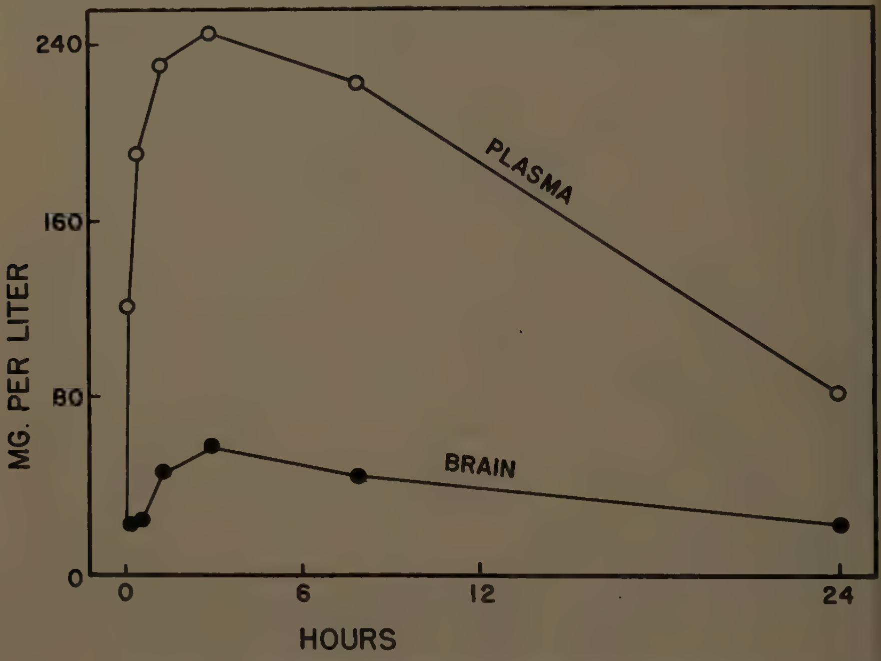

FIGURE 2. Concentration of salicylate in brain and plasma of rats.

Protein Binding

A large part of the salicylate in the blood is bound to plasma proteins. In *in vitro* studies as much as 50 per cent was found to be bound at salicylate concentrations of 200 mg. per cent. Most of the salicylate in the serum is associated with nondiffusible solids of the plasma and, at levels of 200 mg. per cent, only about 30 mg. per cent is diffusible (Smith *et al.*, 1946). Salicylic acid is bound both to bovine and human serum albumin, presumably by 2 types of interaction, the first with few sites and a large association coefficient and the second with more sites but a weak association constant (Davison *et al.*, 1959). The relationship of binding to drug concentration is shown in FIGURE 3 and the relationship to albumin concentration in FIGURE 4. It will be noted that at low drug concentrations and at concentrations of albumin similar to those found in plasma, the fraction of salicylate bound is very high. Under com-

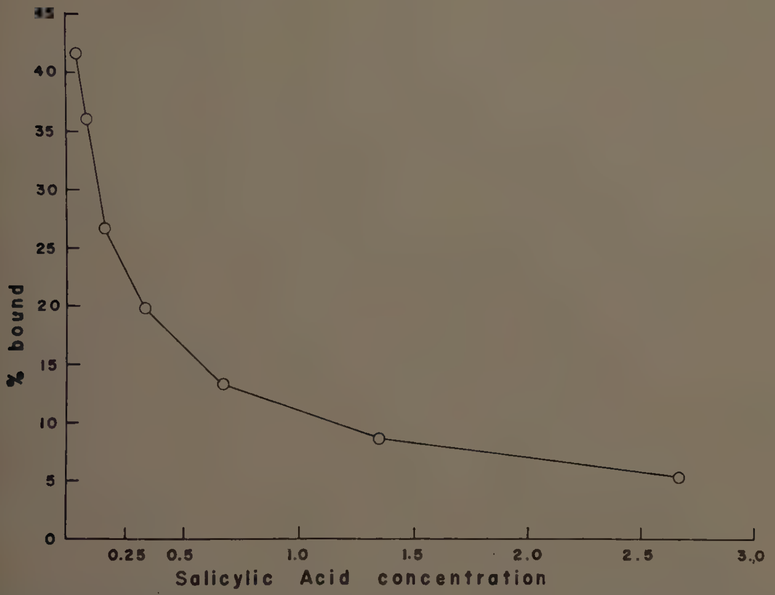

FIGURE 3. Salicylic acid bound to bovine serum albumin (0.1 millimole/l.) at *p*H 7.4, versus millimoles/l. salicylic acid.

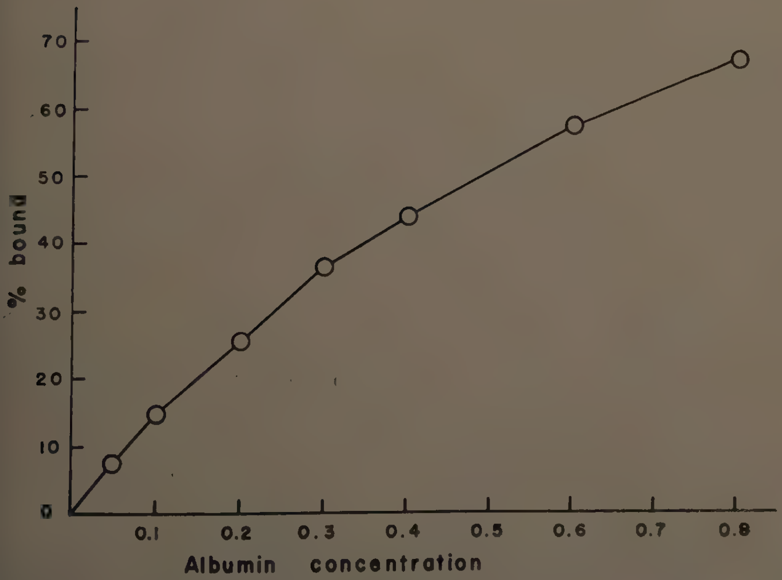

FIGURE 4. Salicylic acid (0.67 millimole/l.) bound to bovine serum albumin at *p*H 7.4, ersus millimoles/l. albumin.

parable circumstances, acetylsalicylate is either not bound or bound to a very limited extent.

Conjugation and Metabolism

The thorough studies of Kapp and Coburn (1942), revealing that children excrete 55 to 60 per cent of salicylate as salicyluric acid, a substance analogous to hippuric acid, leave no doubt that this conjugation product is an important metabolite. Salicyluric acid has no therapeutic effect in rheumatic fever patients and is excreted unchanged. Others (Alpen *et al.*, 1951) have found that the fraction excreted as salicyluric acid is quite variable in the human.

Schayer (1950) found salicylic acid, salicyluric acid, gentisic acid, and two unidentified metabolites in the urine of rats given carboxyl-labeled salicylic acid. A small amount of a fluorescent substance, probably salicyluric acid, has been found in the plasma of dogs given large doses of salicylate (Truitt *et al.*, 1955).

The *in vitro* synthesis of salicyluric acid from salicylic acid and glycine occurred with slices of rat liver and kidney and rabbit liver, but not with dog liver and kidney slices. Salicylic acid inhibited the synthesis of *p*-aminohippuric acid in all tissues studied (Little *et al.*, 1957).

It has long been known that, when salicylates are administered to human patients, reducing substances in the urine other than glucose are increased. Some workers have measured this increase in reducing substances and have ascribed it to glucuronic acid. Alpen *et al.* (1951) synthesized carboxyl-labeled salicylic acid and found that the urinary metabolites in the human included 2 glucuronides (Alpen *et al.*, 1951), one of them an ester glucuronide and the other an ether glucuronide. The amount so excreted varied between 10 and 40 per cent. In more recent studies in man Schachter (1956, 1957) also recovered an ester and a phenolic glucuronide. The ester glucuronide is formed predominately by the human and the ether glucuronide by the rabbit (Robinson and Williams, 1956).

Detectable quantities of one or both glucuronides were formed by slices of intestinal mucosa, liver, kidney, urinary bladder, spleen, and lung. Newborn guinea pig tissue showed only a minimal capacity to form glucuronides, but in three to four days this capacity increased (Schachter *et al.*, 1958). Conjugation was mostly extrarenal. At first there was a more rapid synthesis of acyl glucuronide, then a more rapid synthesis of phenolic glucuronide (Schachter and Manis, 1958).

Prien and Walker (1956) administered acetylsalicylic acid to 19 patients with frequently recurring calcium-containing calculi. In 17 of the patients there was no evidence of increasing calcification. Because these authors believed that the favorable results were due to a combination of the glucuronide with calcium and because they thought more glucuronide was formed after salicylamide administration, they later changed to the latter drug.

Degradation of salicylate to gentisic acid (2,5-dihydroxybenzoic acid) occurs to a small extent (Alpen *et al.*, 1951). When the radiocarbon-labeled material was given to human cancer patients, not more than 1 per cent of the salicylate was recovered as radiocarbon gentisate. Gentisic acid has been isolated from the urine of rats in relatively large amounts after the administration of sodium salicylate, acetylsalicylic acid, and methyl salicylate (Quilley and Smith, 1952). It is not formed in animals whose livers have been damaged by the administration of phosphorus or carbon tetrachloride.

Acetylsalicylic acid differs metabolically from sodium salicylate. Some of it is absorbed unchanged, and unhydrolyzed acetylsalicylic acid has been found in the plasma of human subjects 2 hours after the drug was taken (Lester *et al.*, 1946). After 0.65-gm. doses of acetylsalicylic acid, measurable plasma conconcentrations of salicylic acid may be attained in 10 min. Approximately 30 per cent is present as acetylsalicylic acid (Smith, 1951). Leonards gave aspirin to rats and dogs and found as much as 40 per cent in the plasma as unhydrolyzed aspirin (Leonards, 1958). The presence of aspirin in human plasma after oral administration has been demonstrated conclusively with the use of carboxyl-labeled and acetyl-labeled aspirin (Mandel *et al.*, 1954).

The acetyl group may become a part of the acetate pool; 40 per cent of the radioactivity of acetyl-labeled aspirin is found in the expired air of a rat within 3 hours after the drug is given (Knouse *et al.*, 1951).

Normal human plasma hydrolyzes acetylsalicylic acid fairly readily, dilute solutions being almost completely hydrolyzed in 3 hours. Human erythrocytes are approximately twice as active as the plasma. More than half the aspirin given in low concentrations is split by whole blood in 30 min. The enzyme presumably responsible for this is inhibited partially by physostigmine, but little if at all by cyanide (Smith *et al.*, 1947). The crude enzyme has maximal activity at *p*H 6.0 to 6.5, is readily destroyed by heat, and does not hydrolyze acetamide linkages such as in acetyl-*p*-aminobenzoic acid or acetanilide, but readily hydrolyzes ethyl butyrate. Mulinos and Ardam (1950) observed that aspirin was hydrolyzed by the blood of the rabbit, rat, guinea pig, and dog more readily than by the blood of man. There was partial inhibition by physostigmine.

Methyl salicylate probably is absorbed unchanged. Normal subjects eliminate 45 to 57 per cent of it as substances containing the salicylate radical, but rheumatic fever patients excrete a much more variable percentage. Methyl salicylate is rapidly hydrolyzed by liver tissue from rats, dogs, rabbits, and monkeys. Other tissues hydrolyze the ester more slowly. The reaction is inhibited by diisopropylfluorophosphate (Zimmerman, Davison, and Smith, unpublished).

Excretion

Administered salicylate is excreted primarily in the urine. Up to 95 per cent of the total dose administered is excreted in human patients in the form of compounds containing a salicyl group (Alpen *et al.*, 1951).

It has been known for a long time that patients tolerate salicylates better when sodium bicarbonate is given simultaneously, since the latter lessens the tendency to nausea and vomiting. This beneficial effect of sodium bicarbonate, often attributed to reduction of a local irritating effect on the gastrointestinal tract, is due at least in part to the increased excretion of free salicylate (Smith *et al.*, 1946). When patients are given sodium bicarbonate in addition to the usual dose of sodium salicylate, the plasma concentrations promptly decrease. As soon as sodium bicarbonate is discontinued, the salicylate concentration in the plasma rises rapidly to the previous level. Sodium bicarbonate increases the urinary excretion of salicylate in children to such an extent that the blood levels 4 hours after its administration may be only one half of those attained without sodium bicarbonate. Similar results are obtained during aspirin administration. The renal clearance of salicylates shows a close, though not linear, relationship to the urinary *p*H (Davis and Smith, 1951). The clearance rises slowly with an increase in the urinary *p*H from 5.0 to 7.0 and rapidly with further increasing *p*H. At *p*H 7.8 clearance is approximately 10 times that at *p*H 6.0. Increase of the urinary *p*H from 5.2 to 8.0 results in an increased free salicylate excretion from about 10 per cent to approximately 60 per cent of the total excreted. The excretion of free salicylate increases when the urine is made alkaline either by the administration of sodium bicarbonate or acetazoleamide or by hyperventilation (Macpherson *et al.*, 1955). Thus the excretion depends upon the urinary *p*H and not upon the systemic acid-base balance, since acetazoleamide produces systemic acidosis at the same time that it produces an alkaline urine.

When the urine of dogs is initially acid, acetazoleamide increases the renal clearance of free salicylate but, when the urine is alkaline, it depresses the clearance (Weiner and Mudge, 1959). Schachter and Manis (1958) gave subjects much sodium bicarbonate so that urine was above *p*H 7.5, then gave them probenecid. The clearance of free salicylate fell and was lower than that of creatinine, suggesting reabsorption from alkaline urine.

Clearance studies in rabbits showed that free salicylate was excreted both by filtration and tubular excretion. The tubular excretion could be blocked by the administration of *p*-aminobenzoate (Dalgaard-Mikkelsen, 1951). Tubular secretion was demonstrated in the dog by Weiner *et al.* (1959). Salicylate is secreted by an active transport mechanism, and salicylate and *p*-aminohippuric acid compete for secretion. Secretion is depressed by probenecid.

Related Compounds

Salicylamide, known chemically as *o*-hydroxybenzamide, is not a true salicylate since it does not have a free carboxyl group nor, in the human at least, is it hydrolyzed to salicylate. Accordingly, its pharmacological actions are inherent in the salicylamide molecule and may not be attributed to conversion to salicylate (Mandel *et al.*, 1952). Its early pharmacology and clinical use have been reviewed by Litter *et al.* (1951).

Gentisic acid (2,5-dihydroxybenzoic acid) is formed by the metabolism of salicylate. It was introduced into therapy by Meyer and Ragan (1948). Normally, only a very small quantity is formed in man from salicylate (Alpen *et al.*, 1951). Fevered patients excrete larger quantities of the compound (Quilley and Smith, 1952). The doses of gentisate ordinarily employed in rheumatic fever are of the order of 10 gm. of the sodium salt per day, far in excess of the amount that might be formed in man from therapeutic doses of salicylates. It is now generally recognized that, for this reason, the hypothesis that gentisate formed from salicylate might account for the pharmacological actions of the latter is untenable.

γ-Resorcylic acid is an isomer of gentisic acid. Chemically, the free acid is

2,6-dihydroxybenzoic acid. It has been used experimentally in the therapy of rheumatic fever by Reid *et al.* (1951).

Other compounds related to salicylates that have attracted some attention are 2-ethoxybenzamide and 2-*n*-propoxybenzamide (Bavin *et al.*, 1952), 2-hydroxyisophthalic acid and 4-hydroxyisophthalic acid (Collier and Chesher, 1956), 2,3-dihydroxybenzoic acid (pyrocatechuic acid), and 2,3,6-trihydroxybenzoic acid (Clarke *et al.*, 1958).

Salicylamide has been found to be inferior to aspirin as an antipyretic in rats with induced fever (Buller *et al.*, 1957; Boxhill *et al.*, 1958). 2-Ethoxybenzamide and 2-*n*-propoxybenzamide are more effective antipyretic agents in rats than aspirin or salicylamide (Bavin *et al.*, 1952). 2-Hydroxyisophthalic acid and 4-hydroxyisophthalic acid were antipyretic in rabbits (Collier and Chesher, 1956).

In lower animals salicylamide has a much stronger depressant effect than aspirin, but it does not elicit a state of narcosis. Carlsson and Magnusson (1955) have been unable to demonstrate either an analgesic or antipyretic action of salicylamide.

In rheumatoid arthritis the immediate clinical response to therapy with gentisic acid was excellent in 10 per cent, good in 10 per cent, and only fair in 50 per cent; the initial improvement disappeared in a few days. The results gave no indication that the drug was an adequate therapeutic agent (Rosenberg *et al.*, 1952).

γ-Resorcylic acid is effective in much smaller doses than salicylate in the therapy of rheumatic fever, as judged by clinical, biochemical, and side effects following its administration (Reid *et al.*, 1951). It relieves the acute manifestations of rheumatic fever and is said to give rise to a mild Cushing's syndrome as well as to lead to the same general metabolic changes as those produced by the salicylates.

Ethoxybenzamide is a more potent analgesic than salicylamide (Bavin *et al.*, 1952). The toxicity and analgesic activity of some other cogeners of salicylamide has been described by Way *et al.* (1953). Both 2-hydroxyisophthalic acid and 4-hydroxyisophthalic acid were analgesic in rats (Collier and Chesher, 1956).

Clarke *et al.* (1958) treated rheumatic fever patients with a number of compounds closely related to salicylic acid and observed that antirheumatic potency was greater in compounds with double chelate rings and that compounds with a second or third hydroxyl group in the 3-position, such as pyrocatechuic acid (2,3-dihydroxybenzoic acid) and 2,3,6-trihydroxybenzoic acid were more active. Both the latter compounds were of low toxicity.

Whereas large doses of sodium salicylate inhibited the coronary arteritis produced in rabbits injected with bovine gamma globulin fraction II, the sodium salts of gentisic acid, *m*-hydroxybenzoic acid, *p*-hydroxybenzoic acid, and resorcylic acid and the methyl ester of gentisic acid did not (Moore *et al.*, 1952).

Salicylic acid and acetylsalicylic acid increase the oxygen consumption of rats, but γ-resorcylic acid, gentisic acid, methoxy aspirin, salicylamide, *m*-hydroxybenzoic acid, and *p*-hydroxybenzoic acid do not (Hall *et al.*, 1954). *m*-Hydroxybenzoic acid depresses oxygen consumption (Meade, 1954) and 2,6-

dihydroxybenzoic acid has no effect. Of 18 compounds studied for their metabolic effects in rats, only salicylate and *o*-, *m*-, and *p*-cresotic acids stimulated oxygen consumption. Of these, *o*-cresotic acid was the most powerful, being 2.6 times as strong as salicylate (Andrews, 1958).

Kaplan *et al.* (1954) found that salicylate, gentisate, and γ-resorcylate inhibit the oxidation of succinate. The respiration of rat brain homogenates in the presence of glucose or glutamate is markedly stimulated by 0.015 *M* salicylate, but not by *m*- or *p*-hydroxybenzoic acid (Patel and Heim, 1954). Brain glycolysis is inhibited *in vitro* by aspirin, salicylic acid, gentisic acid, and salicyluric acid and these inhibit the aerobic respiration of brain mitochondria (Penniall *et al.*, 1956).

Salicylate and *m*- and *p*-hydroxybenzoic acid all deplete the ascorbic acid of the adrenal glands of rats, but salicylate is the most potent. Smith (1952*b*) concluded that, since *m*- and *p*-hydroxybenzoic acids are ineffective in rheumatic fever, there is no relation between ascorbic acid depletion and antirheumatic activity. Cronheim *et al.* (1952) found that, in rats, depletion of adrenal ascorbic acid is obtained with benzoate, *p*-methoxy benzoate, gentisate, γ-resorcylate, 5-methoxy salicylate, 3-methylbenzoate, 4-methylbenzoate, 4-chlorobenzoate, 5-chlorobenzoate, 5-sulfonylbenzoate, salicylaldehyde, and salicylamide. There was no significant depletion by *m*-hydroxybenzoate, *p*-hydroxybenzoate, or 4-hydroxysalicylate. The depletion effect was abolished by hypophysectomy. A similar comparative study of the effect of a series of aromatic acids on the ascorbic acid content of the adrenal gland of rats has been reported by Lowenthal and Jaques (1953). Feeney *et al.* (1955) confirmed the observation that salicylates deplete the ascorbic acid of rat adrenals and observed that the effect was greater than that produced by salicylamide or gentisate.

The influence on circulating 17-hydroxycorticosteroid concentrations of a number of compounds structurally related to salicylate has been studied by Done *et al.* (1956). Salicylate and *m*-hydroxybenzoic acid cause a rise, but *p*-hydroxybenzoic acid has no effect.

Feeney *et al.* (1955) observed that salicylates deplete the glycogen of the liver more readily than does salicylamide or gentisate.

When salicylamide is given orally to normal human subjects, it is absorbed and excreted so rapidly that it is difficult to obtain high plasma levels (Seeberg *et al.*, 1951). This problem is complicated further by the fact that it diffuses quickly into the various body tissues and into a much greater apparent volume of body water. It is eliminated rapidly by the kidneys. It is bound to the serum proteins to a much smaller extent than are the salicylates. All these factors result in peak plasma levels after oral administration only one fourth to one eighth as high as those obtained with comparable amounts of salicylate. In human subjects 2 gm. salicylamide gave mean plasma concentrations of 4.8 mg. per cent 1 hour after administration, and this fell to one fourth of this by 4 hours (Hidalgo and Seeberg, 1955). When Weikel (1958) gave human subjects 1.0-gm. doses of acetylsalicylic acid, he found average peak plasma concentrations of 7 mg. per cent of salicylate 3 hours later, but under similar circumstances he found no free salicylamide. In rabbits, salicylamide gave maximal blood levels in 1 hour, and these fell to near zero in 3 to 4 hours (Crampton and Voss, 1954).

Maximal plasma concentrations are reached in 2 hours after the oral administration of single doses of sodium gentisate (Roseman and Dorfman, 1951; Meade and Smith, 1952). When the drug is given orally in doses of 1 gm. every 4 hours, the plasma levels fluctuate from a minimum of 2 mg. per cent to a maximum of 10 mg. per cent 30 min. after administration.

When the salicylamide is labeled with radiocarbon on the carboxyl group, none of it is converted in the human to ordinary salicylate; some is excreted in the free form, but most as a glucuronide (Mandel *et al.*, 1952). Prien and Walker (1955) observed no increase in urinary-tract calculi in 17 of 19 patients given daily doses of 2 gm. acetylsalicylic acid or salicylamide. They attribute the results to complex formation of calcium with the glucuronides formed.

Acidification decreases the excretion of combined gentisate. Alkali increases the excretion of both free and combined gentisate (Batterman and Sommer, 1953). There is no relation between excretion rate and urinary *p*H (Meade and Smith, 1952).

Summary

Salicylates act as antipyretic agents chiefly by increasing heat dissipation through cutaneous vasodilitation. Very large doses may have the opposite effect of raising body temperature.

The analgesic action of salicylates is difficult to demonstrate in animals or in normal human subjects, but it may be observed in carefully controlled studies in patients with pain. The site of the analgesic action has not been defined precisely. The drugs may act centrally, but there is increasing evidence that they reduce pain by reducing the local edema.

Respiration and oxygen consumption are increased by large doses of the salicylates. The resultant loss of carbon dioxide may produce an alkalosis. The respiratory stimulation may be by a central action, but this and the increased oxygen consumption may be the result of a general metabolic stimulation.

The oxygen consumption of most tissues is increased by salicylates. This may be attributed to a dissociation of oxygen utilization and the formation of high-energy phosphate compounds.

While there are reports of the local irritant effects of acetylsalicylic acid on the gastrointestinal tract and of small losses of blood in patients on salicylate therapy, it is not clear whether this is related primarily to the ingestion of aspirin or to the specific preparation used.

Large doses of salicylates stimulate the adrenal glands in experimental animals, but this action may not be related to the therapeutic effects of the drugs in man.

Salicylates reduce the glycosuria and hyperglycemia in experimental diabetic animals and, like insulin, they facilitate the entry of glucose into muscle. In diabetic patients the glycosuria may be abolished and the blood sugar lowered with subsequent clinical improvement. There is an insulin-sparing effect, and the action of synthetic diabetic drugs may be enhanced.

Salicylate and acetylsalicylate are absorbed readily from the stomach, the absorption rate of the former being appreciably faster. The rate of absorption from the small intestine is still greater so that, under clinical conditions, this is the more important site. The rate depends upon the environmental *p*H, being more rapid at greater acidities.

Acetylsalicylic acid may be absorbed unchanged, and appreciable concentrations of it are found in the plasma for some time after administration. It is hydrolyzed readily to ordinary salicylate.

Much of the salicylate in plasma is bound to the albumin. The plasma concentrations are much higher than in the central nervous system.

The metabolites of salicylate in the human are primarily salicyluric acid and the ether and ester glucuronides. Very little gentisic acid is formed.

Excretion is primarily in the urine, the rate of free salicylate excretion being greater at high *p*H values of the urine. There is evidence that free salicylate is removed partially by tubular secretion.

A number of compounds related to the salicylates have been introduced into therapy, but thus far none has been shown to have comparable clinical effectiveness and freedom from undesirable actions.

References

Albanese, A. A., R. A. Higgons, W. H. Arnold & D. R. Hays. 1954. Effect of ACTH, cortisone and salicylates on protein synthesis in man. Federation Proc. **13:** 173.

Alexander, W. D. & K. W. M. Johnson. 1956. A comparison of the effects of acetylsalicylic acid and *dl*-triiodothyronine in patients with myxoedema. Clin. Sci. **15:** 593–601.

Alpen, E. L., H. G. Mandel, V. W. Rodwell & P. K. Smith. 1951. The metabolism of C^{14} carboxyl salicylic acid in the dog and in man. J. Pharmacol. **102:** 150–155.

Alvarez, A. S. & W. H. J. Summerskill. 1958. Gastrointestinal haemorrhage and salicylates. Lancet. **2:** 920–925.

Andrews, M. M. 1958. The relative potencies of some substituted salicylic acids as meta bolic stimulants in the intact rat. Brit. J. Pharmacol. **13:** 419–423.

Bacchus, H. & A. Bacchus. 1953. Effect of aspirin on formalin-arthritis in normal and adrenalectomized rats. Federation Proc. **12:** 7.

Batterman, R. C. & E. M. Sommer. 1953. Fate of gentisic acid in man as influenced by alkalinization and acidification. Proc. Soc. Exptl. Biol. Med. **82:** 376–379.

Bavin, E. M., E. J. Macrae, D. E. Seymour & P. D. Waterhouse. 1952. The analgesic and antipyretic properties of some derivatives of salicylamide. J. Pharm. and Pharmacol. **4:** 872–878.

Bayliss, R. I. S. & A. W. Steinbeck. 1954. Salicylates and the plasma level of adrenal steroids. Lancet. **266:** 1010–1011.

Beecher, H. K. 1957. The measurement of pain. Pharmacol. Rev. **9:** 59–209.

Beecher, H. K., A. S. Keats, F. Mosteller & L. Lasagna. 1953. The effectiveness of oral analgesics (morphine, codeine, acetylsalicylic acid) and the problem of placebo "reactors" and "non-reactors". J. Pharmacol. **109:** 393–400.

Bisset, S. K. & W. D. Alexander. 1958. The effect of sodium salicylate on the oxygen consumption of normal human leucocytes *in vitro*. Biochem. J. **69:** 58.

Bornstein, J., B. W. Meade & M. J. H. Smith. 1952. Salicylates and carbohydrate metabolism. Nature. **169:** 115–116.

Boström, H. & B. Månsson. 1955. The action of salicylates and related compounds on the sulphate exchange of chondroitin sulphuric acid. J. Pharm. and Pharmacol. **7:** 185–190.

Boxhill, G. C., C. B. Nash & A. G. Wheeler. 1958. Comparative pharmacological and toxicological evaluation of *N*-acetyl-*p*-aminophenol, salicylamide and acetylsalicylic acid. J. Am. Pharm. Assoc. Sci. Ed. **47:** 479–487.

Brody, T. M. 1956. Action of sodium salicylate and related compounds on tissue metabolism *in vitro*. J. Pharmacol. **117:** 39–51.

Broh-Kahn, R. H. 1959. Pharmacologic and clinical studies with choline salicylate. Federation Proc. **18:** 17.

Buller, R. H., T. S. Miya & C. J. Carr. 1957. The comparative antipyretic activity of acetylsalicylic acid and salicylamide in fever-induced rats. J. Pharm. and Pharmacol. **9:** 128–133.

Cacchillo, A. F. & W. H. Hassler. 1954. The influence of suppository bases upon the rectal absorption of acetylsalicylic acid. J. Am. Pharm. Assoc. Sci. Ed. **43:** 683–685.

Cameron, J. 1957. The effect of aspirin, cortisone and other compounds on susceptibility to anaphylactic shock in mice. Brit. J. Exptl. Pathol. **38:** 512–514.

Carló, P.-E., N. M. Cambosos, G. C. Feeney & P. K. Smith. 1955. Plasma levels after the oral administration of acetylsalicylic acid and *N*-acetyl-*p*-aminophenol in different forms to human subjects. J. Am. Pharm. Assoc. Sci. Ed. **44:** 396–399.

Carlsson, A. & T. Magnusson. 1955. Failure to demonstrate antipyretic and analgesic properties of salicylamides. Acta Pharmacol. Toxicol. **11:** 248–253.

Cauwenberge, H. van. 1951. Relation of salicylate action to pituitary gland. Observations in rats. Lancet. **261:** 374–375.

Clarke, N. E., C. N. Clarke & R. E. Mosher. 1958. Phenolic compounds in chemotherapy of rheumatic fever. Am. J. Med. Sci. **235:** 7–22.

Coburn, A. F. & J. Haninger. 1954. The serum diphenylamine (DPA) reaction in experimental arthritis. J. Exptl. Med. **99:** 1–19.

Cochran, J. B. 1952. The respiratory effects of salicylate. Brit. Med. J. **2:** 964–967.

Cochran, J. B., R. D. Watson & J. Reid. 1950. Mild Cushing's syndrome due to aspirin. Brit. Med. J. **2:** 1411–1412.

Collier, H. O. J. & G. B. Chesher. 1956. Antipyretic and analgesic properties of two hydroxyisophthalic acids. Brit. J. Pharmacol. **11:** 20–26.

Crabtree, R. E., J. B. Data & J. E. Christian. 1956. A study of the carbon-14 content of blood after the oral administration of C^{14}-carboxyl acetylsalicylic acid to nonfevered and fevered rats. J. Am. Pharm. Assoc. Sci. Ed. **45:** 667–668.

Crampton, J. M. & E. Voss. 1954. Salicylamide I. Absorption, excretion, and blood levels. J. Am. Pharm. Assoc. Sci. Ed. **43:** 470–473.

Crone, C. & U. V. Lassen. 1955a. The effect of salicylic acid and acetylsalicylic acid on uric acid excretion and plasma uric acid concentration in the normal human subject. Acta Pharmacol. Toxicol. **11:** 355–361.

Crone, C. & U. V. Lassen. 1955b. Mechanism of increased renal urate excretion during administration of salicylic acid. Acta Pharmacol. Toxicol. **11:** 362–366.

Cronheim, G., J. S. King, Jr. & N. Hyder. 1952. Effect of salicylic acid and similar compounds on the adrenal-pituitary system. Proc. Soc. Exptl. Biol. Med. **80:** 51–55.

Dalgaard-Mikkelsen, S. 1951. On the renal excretion of salicylate. Acta Pharmacol. Toxicol. **7:** 243–258.

Davis, P. L. & P. K. Smith. 1951. Relation of rate of excretion of salicylate to urinary acidity. Arch. intern. pharmacodynamie. **86:** 303–311.

Davison, C., L. E. Spitzer & P. K. Smith. 1959. The binding of drugs related to salicylic acid by bovine serum albumin. Federation Proc. **18:** 381.

Done, A. K., R. S. Ely & V. C. Kelley. 1954. Studies of 17-hydroxycorticosteroids. III. Blood levels in salicylate intoxication. J. Pediat. **44:** 153–158.

Done, A. K., R. S. Ely & V. C. Kelley. 1955a. Response of plasma 17-hydroxycorticosteroids to salicylate administration in normal human subjects. Metabolism. **4:** 129–142.

Done, A. K., R. S. Ely & V. C. Kelley. 1956. Influence on circulating 17-hydroxycorticosteroid concentrations of compounds structurally related to salicylate. Proc. Soc. Exptl. Biol. Med. **93:** 294–298.

Done, A. K., R. S. Ely & V. C. Kelley. 1958. Salicylates and pituitary-adrenal system. Metabolism. **7:** 52–69.

Done, A. K., R. S. Ely, R. B. Raile & V. C. Kelley. 1955b. Studies of 17-hydroxycorticosteroids. XIII. Effects of salicylate intoxication in rheumatic and nonrheumatic subjects. J. Pediat. **47:** 727–732.

Eckhardt, E. T., M. E. Grelis & I. I. A. Tabachnick. 1958. Effect of some analgesic and anti-inflammatory agents on sodium pentobarbital anesthesia. Proc. Soc. Exptl. Biol. Med. **98:** 423–424.

Ely, R. S., L. E. Ainger, J. R. Seely, A. K. Done & V. C. Kelley. 1955. Studies of 17-hydroxycorticosteroids. X. Urinary excretion of 17-hydroxycorticosteroids in patients with rheumatic fever. J. Clin. Endocrinol. Metabolism. **15:** 523–536.

Farber, H. R., M. J. Yiengst & N. W. Shock. 1949. The effect of therapeutic doses of aspirin on the acid-base balance of the blood in normal adults. Am. J. Med. Sci. **217:** 256–262.

Feeney, G. C., P.-E. Carló & P. K. Smith. 1955. Action of salicylates and related compounds on carbohydrate metabolism and on adrenal ascorbic acid and cholesterol concentrations. J. Pharmacol. **114:** 299–305.

Fishgold, J. T., J. Field & V. E. Hall. 1951. Effect of sodium salicylate and acetylsalicylate on metabolism of rat brain and liver *in vitro*. Am. J. Physiol. **164:** 727–733.

Friend, C. 1953. A study of the effects of sodium salicylate and some structurally related compounds on antigen-antibody reactions *in vitro*. J. Immunol. **70:** 141–146.

George, R. & E. L. Way. 1957. The hypothalamus as an intermediary for pituitary-adrenal activation by aspirin. J. Pharmacol. **119:** 310–315.

Glover, W. E., R. J. Marshall & R. F. Whelan. 1957. The antagonism of the vascular effects of 5-hydroxytryptamine by BOL. 148 and sodium salicylate in the human subject. Brit. J. Pharmacol. **12:** 498–503.

Good, T. A., A. K. Done, R. S. Ely & V. C. Kelley. 1957. Effects of salicylate on plasma 17-hydroxycorticosteroids in hypophysectomized and adrenalectomized guinea pigs. Metabolism. **6:** 346–349.

Graham, J. D. P. & W. A. Parker. 1948. The toxic manifestations of sodium salicylate therapy. Quart. J. Med. **17:** 153–163.

Gross, M. & L. A. Greenberg. 1948. The Salicylates. A Critical Bibliographic Review. Hillhouse Press. New Haven, Conn.

Gruber, C. M., E. P. King, M. M. Best, J. F. Schieve, F. Elkus & E. J. Zmolek. 1956. Clinical bio-assay of oral analgesic activity of propoxyphene (Lilly), acetylsalicylic acid, and codeine phosphate, and observations on placebo reactions. Arch. intern. pharmacodynamie. **104:** 156–166.

Hall, D. E., E. G. Tomich & E. A. Woollett. 1954. Metabolic effect of salicylate. Brit. Med. J. **2:** 99.

Hecht, A. & M. G. Goldner. 1959. Reappraisal of the hypoglycemic action of acetylsalicylate. Metabolism. **8:** 418–428.

Herndon, R., S. Freeman, J. Wheeler & F. Lestina. 1958. The acute effect of acetylsalicylic acid in man. Arch. Intern. Med. **101:** 623–629.

Hetzel, B. S., J. S. Charnock & H. Lander. 1959. Metabolic effects of salicylate in man. Metabolism. **8:** 205–213.

Hetzel, B. S. & D. C. Hine. 1951. The effect of salicylates on the pituitary and suprarenal glands. Lancet. **261:** 94–97.

Hidalgo, J. & V. P. Seeberg. 1955. A note on serum levels and excretion of salicylamide in man. J. Am. Pharm. Assoc. Sci. Ed. **44:** 384.

Hill, A. G. S. 1952. C-reactive protein in rheumatic fever. Lancet. **263:** 558–560.

Hogben, C. A. M., L. S. Schanker, D. J. Tocco & B. B. Brodie. 1957. Absorption of drugs from the stomach. II. The human. J. Pharmacol. **120:** 540–545.

Hogben, C. A. M., D. J. Tocco, B. B. Brodie & L. S. Schanker. 1959. On the mechanism of intestinal absorption of drugs. J. Pharmacol. **125:** 275–282.

Ingle, D. J. 1953. Effects of aspirin, aminopyrine, and HPC upon glucosuria in the diabetic rat. J. Am. Pharm. Assoc. Sci. Ed. **42:** 247–249.

Ingle, D. J. & R. C. Meeks. 1952. Suppression of glycosuria during administration of large doses of aspirin to force-fed partially depancreatectomized rats. Am. J. Physiol. **171:** 600–603.

Ingle, D. J., D. F. Beary & A. Purmalis. 1953. The effect of aspirin upon the glycosuria and partially depancreatized rats in the presence and absence of the adrenal glands. Endocrinology. **52:** 403–406.

Kaplan, E. H., J. Kennedy & J. Davis. 1954. Effects of salicylate and other benzoates on oxidative enzymes of the tricarboxylic acid cycle in rat tissue homogenates. Arch. Biochem. Biophys. **51:** 47–61.

Kapp, E. M. & A. E. Coburn. 1942. Urinary metabolites of sodium salicylate. J. Biol. Chem. **145:** 549–565.

Kelemen, E. 1957. The inhibition by sodium salicylate of oedema of the hind-paw of the rat induced by 5-hydroxytryptamine. Brit. J. Pharmacol. **12:** 28–29.

Kelley, J. J., Jr. 1956. Salicylate ingestion: A frequent cause of gastric hemorrhage. Am. J. Med. Sci. **232:** 119–127.

Knouse, R. W., W. D. Paul & J. I. Routh. 1951. Fate of C^{14}-labeled acetylsalicylic acid. Federation Proc. **10:** 209–210.

Leonards, J. R. 1958. Absorption of aspirin from the gastrointestinal tract. Federation Proc. **17:** 262.

Lepper, M. H., E. R. Caldwell, P. K. Smith & B. F. Miller. 1950. Effects on anaphylactic shock of salicylates, aminopyrine and other chemically and pharmacologically related compounds. Proc. Soc. Exptl. Biol. Med. **74:** 254–258.

Lester, D., G. Lolli & L. A. Greenberg. 1946. The fate of acetylsalicylic acid. J. Pharmacol. **87:** 329–342.

Litter, M., A. R. Moreno & L. Donin. 1951. Salicylamide: pharmacology, fate and clinical use. J. Pharmacol. **101:** 119–124.

Little, J. M., E. A. Angell & A. M. Morgan. 1957. *In vitro* synthesis of *p*-aminohippurate in the dog, rat, and rabbit as affected by sodium salicylate. Arch. intern. pharmacodynamie. **111:** 259–265.

Little, J. M., E. R. Strader & E. B. Truitt, Jr. 1954. The relation between the structure of halogenated benzoic acids and the depletion of adrenal ascorbic acid content. J. Pharmacol. **112:** 378–381.

Lowenthal, J. & L. B. Jaques. 1953. A comparative study of the effect of a series of aromatic acids on the ascorbic acid content of the adrenal gland. J. Pharmacol. **107:** 172–177.

Macpherson, C. R., M. D. Milne & B. M. Evans. 1955. The excretion of salicylate. Brit. J. Pharmacol. **10:** 484–489.

Manchester, K. L., P. J. Randle & G. H. Smith. 1958. Some effects of sodium salicylate on muscle metabolism. Brit. Med. J. **1:** 1028–1030.

Mandel, H. G., N. M. Cambosos & P. K. Smith. 1954. The presence of aspirin in human plasma after oral administration. J. Pharmacol. **112:** 495–500.

Mandel, H. G., V. W. Rodwell & P. K. Smith. 1952. A study of the metabolism of C-14 salicylamide in the human. J. Pharmacol. **106:** 433–439.

Manso, D., A. Taranta & I. Nydick. 1956. Effect of aspirin administration on serum glutamic oxaloacetic and glutamic pyruvic transaminases in children. Proc. Soc. Exptl. Biol. Med. **93:** 84–88.

Marson, F. G. W. 1954. Sodium salicylate and probenecid in the treatment of chronic gout; assessment of their relative effects in lowering serum uric acid levels. Ann. Rheumat. Disease. **13:** 233–245.

Matsumoto, K. K. & M. I. Grossman. 1959. Quantitative measurement of gastrointestinal blood loss during ingestion of aspirin. Proc. Soc. Exptl. Biol. Med. **102:** 517–519.

Meade, B. W. 1954. Effect of certain hydroxybenzoic acids on the oxygen consumption of Wistar rats. Ann. Rheumatic Disease. **13:** 60–62.

Meade, B. W. & M. J. H. Smith. 1952. Factors influencing plasma concentrations of gentisate. Clin. Sci. **11:** 81–89.

Messer, M. 1958. A comparison of the effects of barbiturates, salicylates, chlorpromazine, 2,4-dinitrophenol and cyanide on the synthesis of glutamine by brain cells *in vitro.* Austral. J. Exptl. Biol. Med. Sci. **36:** 65–76.

Meyer, R. & C. Ragan. 1948. The antirheumatic effect of sodium gentisate. Science. **108:** 281.

Miller, R. H. & S. M. Tenney. 1956. Action of sodium salicylate on tissue gas tensions. Proc. Soc. Exptl. Biol. Med. **92:** 791–793.

Moore, D. F., J. Lowenthal, M. Fuller & L. B. Jaques. 1952. Inhibition of experimental arteritis by cortisone, salicylate and related compounds. Am. J. Clin. Pathol. **22:** 936–943.

Mulinos, M. G. & I. Ardam. 1950. An aspirin splitting enzyme in blood. J. Pharmacol. **98:** 23–24.

Muir, A. & I. A. Cossar. 1955. Aspirin and ulcer. Brit. Med. J. **2:** 7–12.

Nayler, W. G. 1957. The action of salicylate, dinitrophenol and cardiac glycosides on the isolated toad heart. Austral. J. Exptl. Biol. Med. Sci. **35:** 491–498.

Orkin, L. R., S. I. Joseph & M. Helrich. 1957. Effects of mild analgesics on postpartum pain: A method for evaluating analgesics. N. Y. State Med. J. **57:** 71–73.

Parker, W. A. 1948. Factors influencing plasma concentrations of salicylate. Quart. J. Med. **17:** 229–246.

Patel, C. A. & H. C. Heim. 1954. The effect of the monohydroxy benzoic acids on the respiration of rat brain homogenates. J. Am. Pharm. Assoc. Sci. Ed. **43:** 251–253.

Penniall, R. 1958. The effects of salicylic acid on the respiratory activity of mitochondria. Biochem. Biophys. Acta. **30:** 247–251.

Penniall, R., G. Kalnitsky & J. I. Routh. 1956. The effects of salicylic acid and related compounds on *in vitro* rat brain respiration. Arch. Biochem. Biophys. **64:** 390–400.

Poulsen, H. 1955. Inhibition of uric acid excretion in rabbits given probenecid or salicylic acid. Acta Pharmacol. Toxicol. **11:** 277–286.

Prien, E. L. & B. S. Walker. 1955. Salicylate therapy of recurrent calcium urolithiasis. New Engl. J. Med. **253:** 446–451.

Prien, E. L. & B. S. Walker. 1956. Salicylamide and acetylsalicylic acid in recurrent urolithiasis. J. Am. Med. Assoc. **160:** 355–360.

Quilley, E. & M. J. H. Smith. 1952. The application of paper partition chromatography to the study of the metabolism of salicylate in the rat. J. Pharm. and Pharmacol. **4:** 624–630.

Randall, L. O. & J. J. Selitto. 1957. A method for measurement of analgesic activity of inflamed tissue. Arch. intern. pharmacodynamie. **111:** 409–419.

Randle, P. J. & G. H. Smith. 1958a. Regulation of glucose uptake by muscle. I. The effects of insulin, anaerobiosis and cell poisons on the uptake of glucose and release of potassium by isolated rat diaphragm. Biochem. J. **70:** 490–500.

Randle, P. J. & G. H. Smith. 1958b. Regulation of glucose uptake by muscle. II. The effects of insulin, anaerobiosis and cell poisons on the penetration of isolated rat diaphragm by sugars. Biochem. J. **70:** 501–508.

Reid, J. 1957. Comparison of salicylate and 2:4-dinitrophenol on the growth of wheat coleoptiles. Nature. **179:** 484–485.

Reid, J., A. I. MacDougall & M. M. Andrews. 1957. Aspirin and diabetes mellitus. Brit. Med. J. **2:** 1071–1074.

Reid, J., R. D. Watson, J. B. Cochran & D. H. Sproull. 1951. Sodium γ-resorcylate in rheumatic fever. Brit. Med. J. **1:** 321–324.

Reid, J., R. D. Watson & D. H. Sproull. 1950. The mode of action of salicylate in acute rheumatic fever. Quart. J. Med. **19:** 1–19.

Robinson, D. & R. T. Williams. 1956. Glucuronides of salicylic acid. Biochem. J. **62:** 23P.

Roseman, S. & A. Dorfman. 1951. The determination and metabolism of gentisic acid. J. Biol. Chem. **192:** 105–114.

Rosenberg, E. F., D. A. Krevsky & B. M. Kagan. 1952. Laboratory and clinical experience with sodium gentisate in rheumatic disease. Ann. Intern. Med. **36:** 1513–1519.

Schachter, D. 1956. Chemical estimation of acyl glucuronides: formation and urinary excretion in the human. Federation Proc. **15:** 479–480.

Schachter, D. 1957. The chemical estimation of acyl glucuronides and its application to studies on the metabolism of benzoate and salicylate in man. J. Clin. Invest. **36:** 297–302.

Schachter, D., D. J. Kass & T. J. Lannon. 1958. Biosynthesis of salicyl glucuronides *in vitro*. Federation Proc. **17:** 304.

Schachter, D. & J. G. Manis. 1958. Salicylate and salicyl conjugates; fluorimetric estimation, biosynthesis and renal excretion in man. J. Clin. Invest. **37:** 800–807.

Schanker, L. S., B. B. Brodie & C. A. M. Hogben. 1958b. Drug absorption by the large intestine. J. Pharmacol. **122:** 66A–67A.

Schanker, L. S., P. A. Shore, B. B. Brodie & C. A. M. Hogben. 1957. Absorption of drugs from the stomach. I. The rat. J. Pharmacol. **120:** 528–539.

Schanker, L. S., D. J. Tocco, B. B. Brodie & C. A. M. Hogben. 1958a. Absorption of drugs from the rat small intestine. J. Pharmacol. **123:** 81–88.

Schayer, R. W. 1950. The metabolism of radioactive salicylic acid. Arch. Biochem. **28:** 371–376.

Seeberg, V. P., D. Hansen & B. Whitney. 1951. Absorption and distribution of salicylamide. J. Pharmacol. Exptl. Therap. **101:** 275–282.

Seely, J. R., R. S. Ely, A. K. Done, L. E. Ainger & V. C. Kelley. 1955. Studies of 17-hydroxycorticosteroids. VII. Effects of therapy on concentration of 17-hydroxycorticosteroids in the plasma of patients with rheumatic fever. Pediatrics. **15:** 543–552.

Segar, W. E. & M. A. Holliday. 1958. Physiologic abnormalities of salicylate intoxication. New Engl. J. Med. **259:** 1191–1198.

Shwartzman, G. & S. S. Schneierson. 1953. Inhibition of the phenomenon of local tissue reactivity by corticosteroids, salicylates, and compounds related to salicylates. Ann. N. Y. Acad. Sci. **564:** 733–736.

Singer, R. B. 1954. The acid-base disturbance in salicylate intoxication. Medicine. **33:** 1–13.

Smith, M. J. H. 1951. Plasma-salicylate concentrations after small doses of acetylsalicylic acid. J. Pharm. and Pharmacol. **3:** 409–414.

Smith, M. J. H. 1952a. The effect of salicylate on the glycosuria and hyperglycaemia induced by cortisone in the normal rat. Biochem. J. **52:** 649–652.

Smith, M. J. H. 1952b. Monohydroxybenzoic acids and ascorbic acid depletion of the adrenal glands in the intact rat. Lancet. **262:** 991–993.

Smith, M. J. H. 1953. Some recent advances in the pharmacology of salicylates. J. Pharm. and Pharmacol. **5:** 81–93.

Smith, M. J. H. 1954a. The effect of salicylate on liver glycogen, blood glucose and the passage of a barium meal in the rat. Biochem. J. **57:** vii.

Smith, M. J. H. 1954b. The effect of salicylate on liver glycogen in the rat. Biochem. J. **57:** 349–352.

Smith, M. J. H. 1954c. The effect of salicylate on glucose tolerance in the rat. Biochim. et Biophys. Acta. **14:** 241–245.

Smith, M. J. H. 1955a. The effects of sodium salicylate on blood glucose in the rat. Brit. J. Pharmacol. **10:** 111–112.

Smith, M. J. H. 1955b. The effects of salicylate and adrenocortical preparations added *in vitro* upon the glycogen content of liver slices. Biochem. J. **59:** 52–55.

Smith, M. J. H. 1958a. Effects of salicylate on the metabolic activity of the small intestine of the rat. Am. J. Physiol. **193:** 29–33.

Smith, M. J. H. 1958b. Action of salicylate on metabolism of acetate-2-C^{14} in the rat. Science. **128:** 423.

Smith, M. J. H. 1959. Salicylates and metabolism. J. Pharm. and Pharmacol. **11:** 705–720.

Smith, M. J. H., C. H. Gray & J. B. Lunnon. 1954a. Urinary excretion of adrenocortical steroids by patients receiving salicylates. Lancet. **266:** 1008–1009.

Smith, M. J. H., C. H. Gray & J. B. Lunnon. 1954b. The excretion of urinary adrenocortical steroids in patients treated with salicylates. J. Endocrinol. **10:** xvii–xviii.

Smith, M. J. H. & J. D. Irving. 1955. The effect of salicylate on the passage of a barium meal in the rat. Brit. J. Radiol. **28:** 39–41.

Smith, M. J. H. & S. W. Jeffrey. 1956a. Salicylate and carbohydrate metabolism. Nature. **178:** 310.

Smith, M. J. H. & S. W. Jeffrey. 1956b. The effects of salicylate on oxygen consumption and carbohydrate metabolism in the isolated rat diaphragm. Biochem. J. **63:** 524–528.

Smith, M. J. H., B. W. Meade & J. Bornstein. 1952. The effect of salicylate on glycosuria blood glucose and liver glycogen of the alloxan-diabetic rat. Biochem. J. **51:** 18–20.

Smith, P. K. 1949. Certain aspects of the pharmacology of the salicylates. Pharmacol. Rev. **1:** 353–382.

Smith, P. K. 1958. Nonnarcotic analgesics and antipyretics. I. Salicylates. *In* Pharmacology in Medicine. : 253–271. V. A. Drill, Ed. McGraw-Hill. New York, N.Y.

Smith, P. K., H. L. Gleason, C. G. Stoll & S. Orgorzalek. 1946. Studies on the pharmacology of salicylates. J. Pharmacol. **87:** 237–255.

Smith, P. K., H. A. Hand & R. J. Madden. 1947. The hydrolysis of acetylsalicylic acid by animal tissues. Federation Proc. **6:** 373.

Sproull, D. H. 1954a. The glycogenolytic action of sodium salicylate. Brit. J. Pharmacol. **9:** 121–124.

Sproull, D. H. 1954b. A peripheral action of sodium salicylate. Brit. J. Pharmacol. **9:** 262–264.

Stephenson, N. R. 1958. Effect of salicylates on thymus gland of immature rat. Federation Proc. **17:** 316.

Stolzer, B. L., H. B. Houser & E. J. Clark. 1954. Comparative effects of aspirin, ACTH and cortisone on the antistreptolysin "O" titer and gamma globulin concentration in rheumatic fever. J. Lab. Clin. Med. **44:** 229–234.

Stubbé, L. T. F. L. 1958. Occult blood in faeces after administration of aspirin. Brit. Med. J. **2:** 1062–1066.

Summerskill, W. H. J. & A. S. Alvarez. 1958. "Salicylate anaemia." Lancet. **2:** 925–928.

Tenney, S. M. & R. M. Miller. 1955. The respiratory and circulatory actions of salicylate. Am. J. Med. **19:** 498–508.

Truitt, E. B., Jr. & A. M. Morgan. 1958. Absorption of aspirin and buffered aspirin from the stomach in man. Federation Proc. **17:** 415.

Truitt, E. B., Jr., A. M. Morgan & J. M. Little. 1955. Determination of salicylic acid and two metabolites in plasma and urine using fluorimetry for directly measuring salicyluric acid. J. Am. Pharm. Assoc. Sci. Ed. **44:** 142–148.

Walton, R. P. & T. D. Darby. 1958. Circulatory effects of salicylates. Circulation Research. **6:** 155–158.

Way, E. L., A. E. Takemori, G. E. Smith, Jr., H. H. Anderson & D. C. Brodie. 1953. The toxicity and analgetic activity of some congeners of salicylamide. J. Pharmacol. **108:** 450–460.

Weikel, J. H. 1958. A comparison of human serum levels of acetylsalicylic acid, salicylamide, and *N*-acetyl-*p*-aminophenol following oral administration. J. Am. Pharm. Assoc. Sci. Ed. **47:** 477–479.

Weiner, I. M. & G. H. Mudge. 1959. Effect of acetazoleamide on the renal mechanism of salicylate excretion in dogs. Federation Proc. **18:** 166.

Weiner, I. M., J. A. Washington II & G. H. Mudge. 1959. Studies on the renal excretion of salicylate in the dog. Bull. Johns Hopkins Hosp. **105:** 284–297.

Whitehead, P. L. & D. M. Woodbury. 1958. Central nervous system effects of Na salicylate in relation to electrolyte and acid-base metabolism. Proc. Am. Soc. Pharmacol. Fall Meeting. Ann Arbor, Mich. : 38c.

Winters, R. W. & M. F. Morrill. 1955. Carbohydrate metabolism in experimental salicylism. Proc. Soc. Exptl. Biol. Med. **88:** 409–411.

Wolf, J. & R. Aboody. 1959. Studies on the rate of absorption of the choline salt of salicylic acid. Federation Proc. **18:** 605.

THERAPEUTIC PROPERTIES OF SALICYLATE AND ITS MODE OF ACTION

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It is customary to think of a specific remedy for a specific disease. Hence a drug possessing several therapeutic properties is viewed with both interest and suspicion. The remarkable therapeutic versatility of salicylate will be considered in this paper; also, its well-known therapeutic action in rheumatic fever and its effects in abnormal metabolic states such as myxedema, hypercholesterolemia, and diabetes mellitus will be discussed. However, it should be understood at the outset that at present these other uses are of research interest and are not established forms of treatment.

The mode of action of salicylate in rheumatic fever is still not known. Clinicians in the first quarter of the century were led to postulate a central action on the brain in spite of the fact that the pharmacological actions of the drug, as recently reviewed and extended by Smith,[1] are peripheral as well. The next therapeutic landmark was the clear demonstration by Coburn[2] of the importance of maintaining an adequate level of the drug in the blood for effective treatment. This was the background of information at the start of the work described in this paper. The first task was to become familiar with the effects of the drug on salient features of the disease.

A particularly good response to full salicylate treatment is illustrated in FIGURE 1. The striking features in this case were the rapid fall in E.S.R., which serves as an empirical index of rheumatic activity, and the progressive rise in output of urine in a patient receiving a constant fluid intake. This rise in urinary output, culminating in diuresis, suggested that an abnormal water distribution may be a significant abnormality in the acute rheumatic state.[3]

The relationship of joint pain and joint swelling to the effect of salicylate therapy is demonstrated in FIGURE 2. This study was carried out in patients with acute arthritis involving the knee joints, because the circumference of this joint may readily be measured and taken as an index of joint swelling. The prompt and simultaneous subsidence of pain and swelling immediately following salicylate therapy is invariable, and it suggests that pain and swelling are intimately related to one another. The rapid disappearance of joint pain and swelling and the complete return to normal function immediately following salicylate therapy suggest that reversible local vascular changes and derangement in distribution of water in the tissues may be essential abnormalities in the joints in rheumatic fever. This possibility has been studied further during the first few hours of salicylate treatment, when rapid changes in body weight may be taken as a measure of over-all changes in body water. Patients were fasted before and for several hours after the beginning of salicylate therapy. They had no desire for food, but were given measured quantities of water and were weighed carefully every two hours when pulmonary ventilation and oxygen consumption measurements were also made to allow for food consumption. With these data and a knowledge of the fluid loss through other channels it was possible to calculate and compare the loss of water through sweating and respiration immediately before and after salicylate therapy. The results obtained in this experiment are illustrated in a typical case in FIGURE 3. The sharp defervescence and immediate increase in water loss through sweating that follow salicylate administration are noteworthy. Simultaneous relief of joint pain and swelling also accompany the sweating. These findings, in conjunction with our previous results, indicate that the immediate antipyretic action of salicylate in rheumatic fever is at least partly due to heat loss through sweating, although a direct action on the factor responsible for fever cannot be excluded. Joint pain is relieved through reduction in joint swelling through a peripheral action on the joints, and swelling may also disappear from water loss, chiefly through sweating.

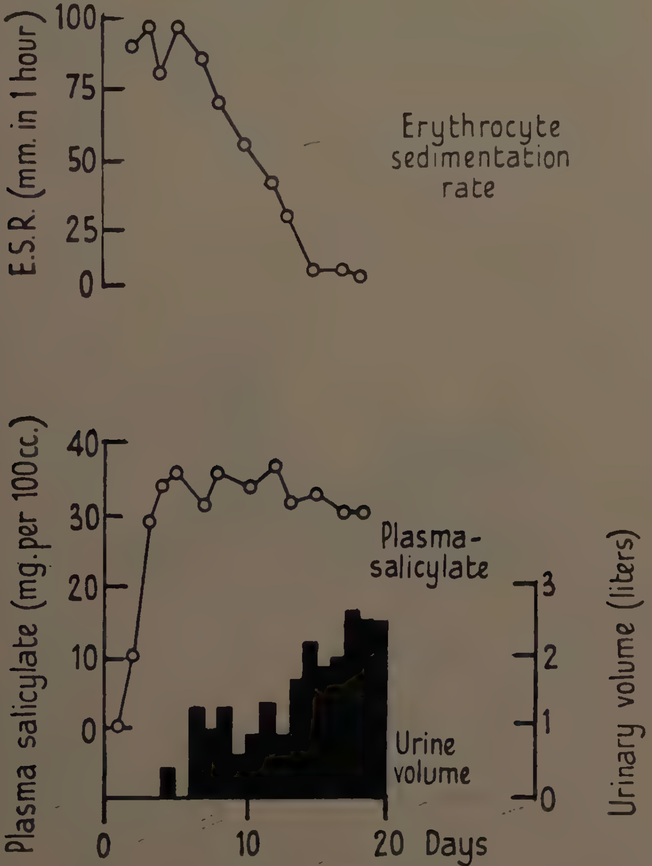

FIGURE 1. The sharp fall in E.S.R. and the progressive rise in urine output of a patient receiving a constant fluid intake during salicylate therapy of rheumatic fever. Reproduced by permission from *The Quarterly Journal of Medicine*.[17]

A clue to the direction of changes in body water was provided by nitrogen and potassium balance studies carried on throughout the course of the disease.

From the beginning of salicylate treatment, nitrogen and potassium excretion increase progressively to values greater than the dietary intake of both, simultaneously with disappearance of fever and of arthritis.[3] These changes are usually accompanied by removal of water from tissues, a suggestion supported by the clinical development of dry tongue and other signs of tissue dehydration when too much salicylate is given. The early changes in urinary excretion of sodium and potassium in relation to joint pain, fever, and sweating are shown in FIGURE 4.

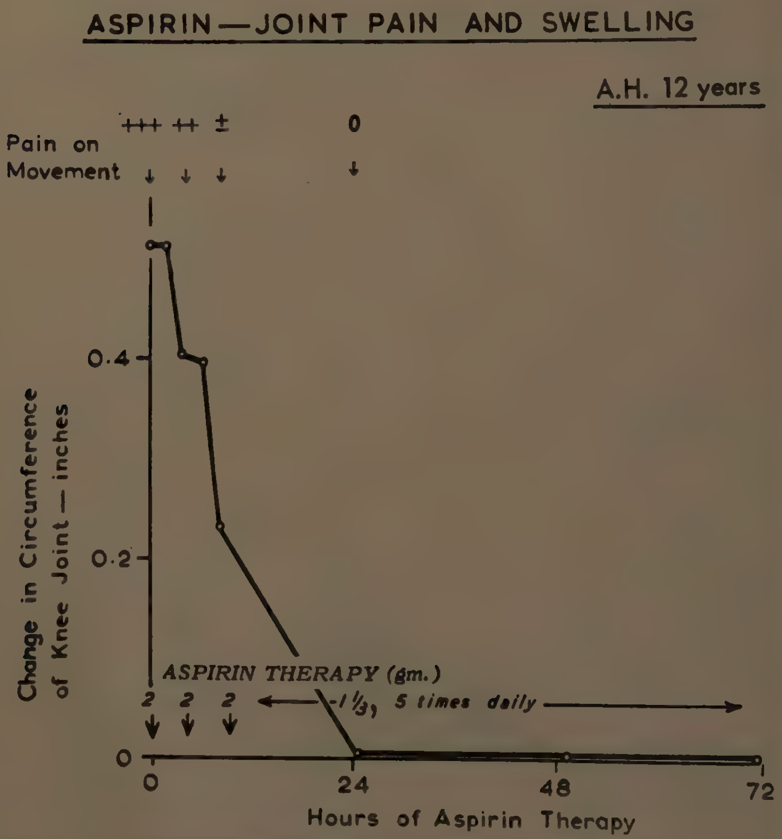

FIGURE 2. Simultaneous disappearance of joint pain and joint swelling in a patient receiving frequent doses of aspirin to build up an effective plasma level of the drug.

While reversal of local vascular changes and abnormal water distribution may explain the analgesic action of salicylate in rheumatic fever, a high plasma fibrinogen concentration is also a noteworthy feature of the disease, as shown by Ernstene.[4] My colleague and I have extended his observation and have found that the severity of an attack of rheumatic fever is related more or less directly to the fibrinogen level.[5] Moreover, the high fibrinogen level accounts in the main for the rise in the E.S.R. The relapsing nature of the disease and the therapeutic action of salicylate on the chief clinical and biochemical features are illustrated in FIGURE 5.

The effect of salicylate on the high plasma fibrinogen is most striking. It is invariable, and it is therapeutically important in that the high fibrinogen is almost certainly an integral part of the rheumatic disease process, the gross pathology of which is so characterized by massive fibrin deposition in pericardium, joints, and even in the lungs themselves.

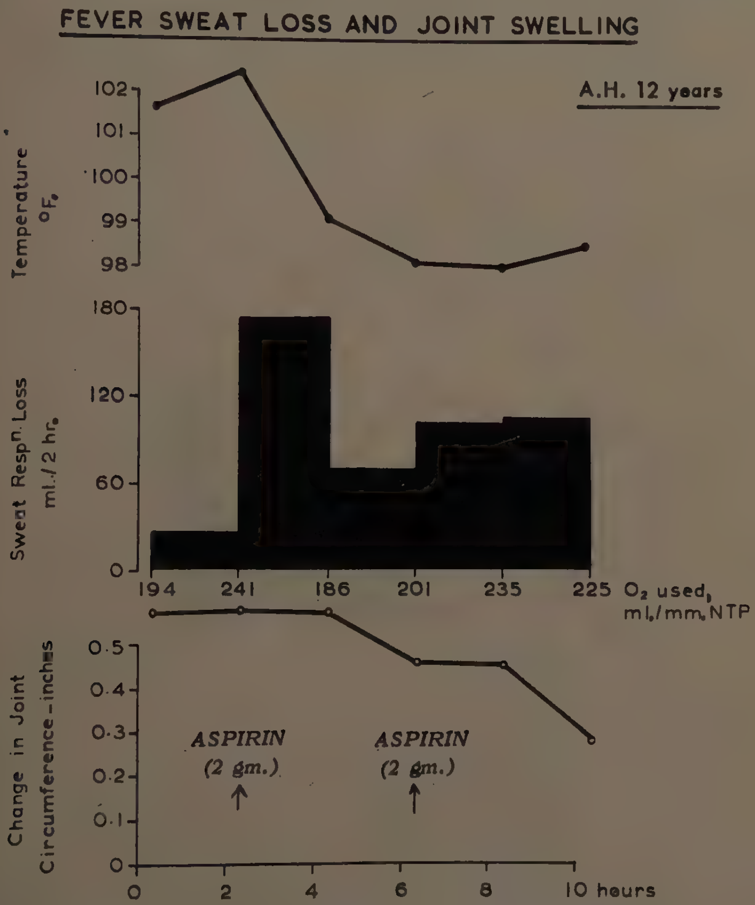

FIGURE 3. Subsidence of fever and reduction of joint swelling following sweating induced by aspirin.

It is worth noting, in passing, the accepted action of the drug in gout and also a newer application of it in resistant forms of psoriasis associated with chronic rheumatism. The effect on the raised blood uric acid in gout is demonstrated in FIGURE 6. The patient was kept on a low purine diet. At the end of a control period, administration of salicylate in full doses was begun. The rapid fall in blood uric acid associated with its increased urinary excretion are shown together with the serum salicylate concentrations throughout the period of treatment.

The effect of full salicylate therapy on a form of psoriasis most resistant to orthodox treatment is shown in the photographs taken before and one month after initiation of treatment. The reduction in erythema and the growth of normal nails were most striking (FIGURES 7 and 8).

An outstanding biological property of salicylate is its ability to stimulate

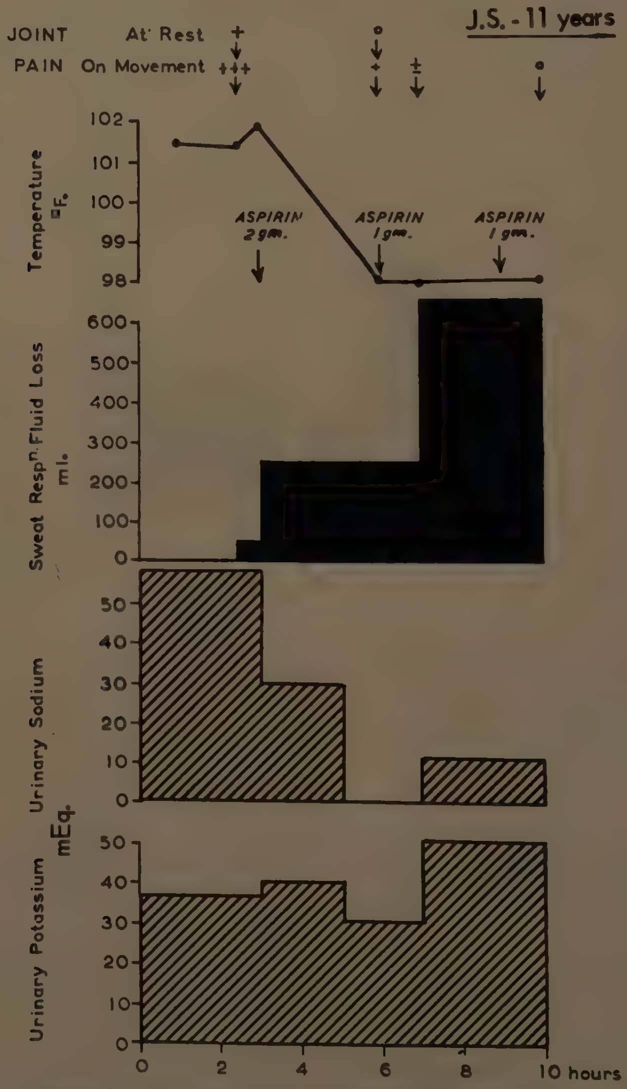

FIGURE 4. Changes in urinary sodium and potassium in relation to relief of joint pain, subsidence of fever, and the great increase in sweating induced by aspirin.

oxygen consumption in plants, animals,[6,7] and man.[8,9] This property is not confined to the intact organism, for it has been demonstrated clearly by Sproull[10] that oxygen consumption in brain, liver, and kidney cells *in vitro* rises in the presence of salicylate, establishing the fact that this compound has a definite peripheral action.

This finding makes possible consideration of other therapeutic aspects of the drug, such as its metabolism-stimulating properties in myxedema. Alexander and Johnson[11] have studied the effects of aspirin in this disease and found that symptoms due to depressed metabolism, such as coldness in the extremities and cramps, were relieved, but that other characteristic features were unaltered. Quite unexpectedly, however, patients who had myxedema and also angina pectoris obtained relief from anginal pain while they were receiving salicylate. A subjective finding such as this is difficult to evaluate, but in cases where administration of the drug coincided with a lowering of the blood cholesterol level to normal, it merited further study. Observation was extended, and it was found that salicylate lowered hypercholesterolemia in general and was

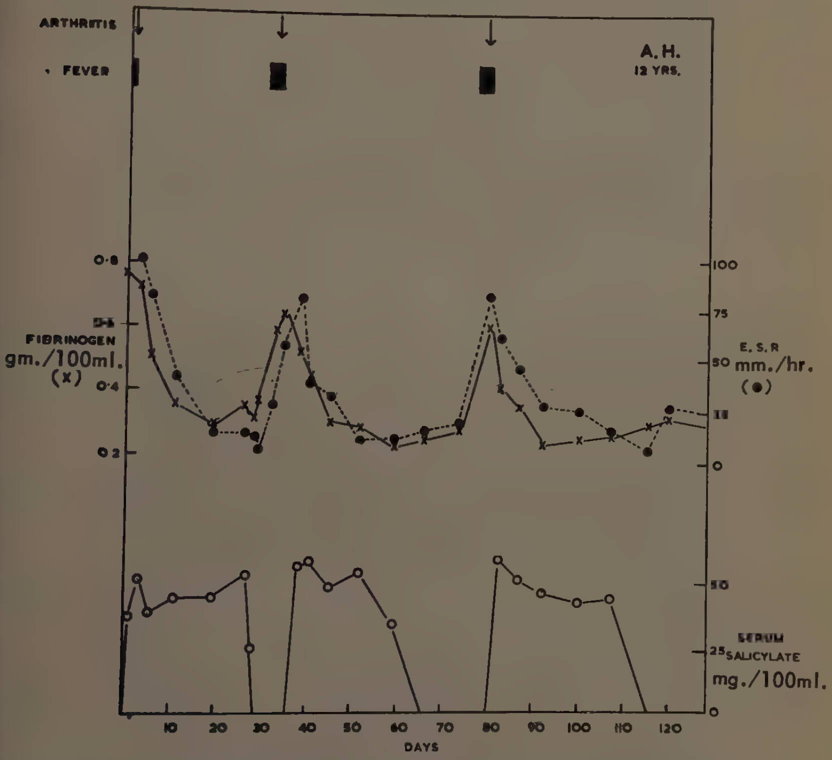

FIGURE 5. The relapsing nature of rheumatic fever and the effect of salicylate in suppressing attacks. The close relation of the E.S.R. to the plasma fibrinogen level, and the effect of aspirin on both are noteworthy. Reproduced by permission from *British Medical Journal*.[5]

as effective as thyroid hormones in this respect. Recently it has also been established that salicylate lowers hypercholesterolemia in coronary disease, but that the high incidence of side effects weighs against it as a practical form of treatment.[12] The drug's research potential nevertheless remains.

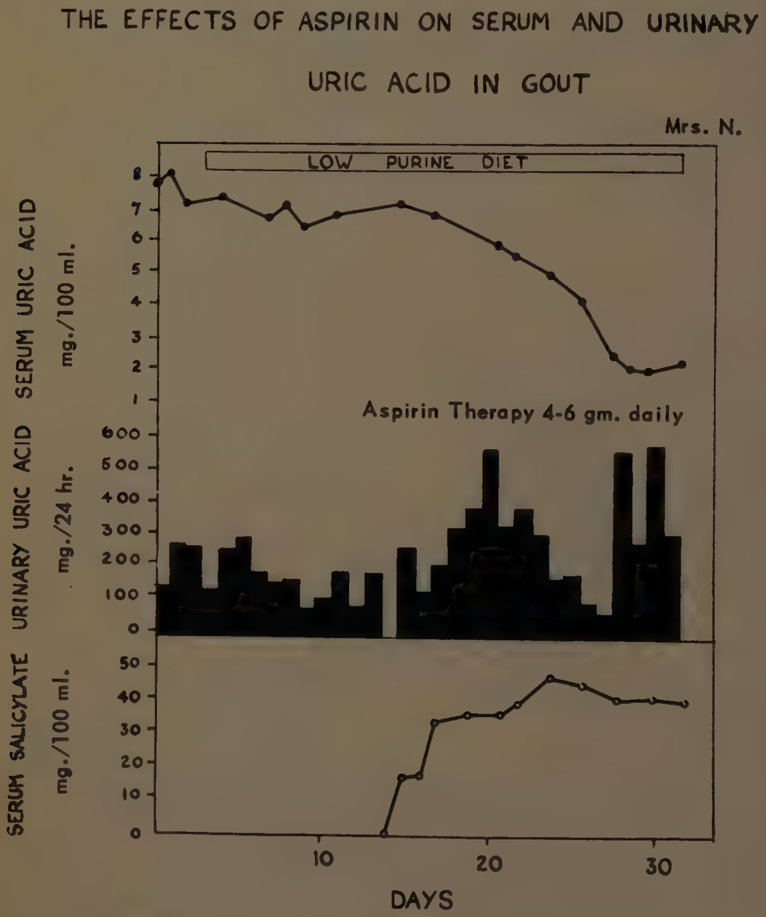

Figure 6. Lowering of serum uric acid and its increased excretion in urine of a patient receiving aspirin therapy and kept on a constant low purine diet.

Finally, salicylate is therapeutically active in diabetes mellitus, as has been established clearly in animals by Ingle[13] and confirmed by Smith.[14] In diabetic patients it reduces blood sugar and glycosuria, controls moderately severe ketosis, and improves glucose tolerance.[15] Full doses have an insulin equivalence of as much as 30 U. lente insulin daily.[16]

Salicylate or a derivative may prove useful in controlling moderately severe diabetes in elderly patients who do not wish insulin injections, and its simultaneous effect on hypercholesterolemia may be beneficial in a disease in which vascular degeneration is so common. Another possible use lies at the other

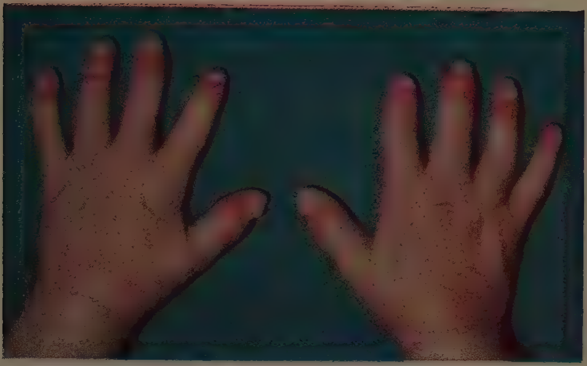

FIGURE 7. Appearance of the fingers and nails immediately before aspirin therapy.

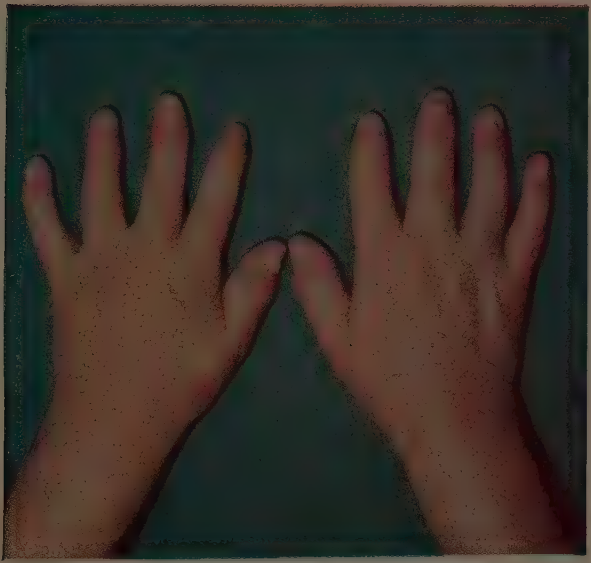

FIGURE 8. Reduction of erythema and the growth of normal new nail after treatment for one month with full doses of salicylate.

end of the scale, for diabetics who require very large doses of insulin and are troubled with hypoglycemic attacks. Reduction of the insulin requirement by about 60 U. and combined insulin-aspirin therapy reduces susceptibility to these attacks.

Salicylate's remarkable therapeutic versatility is both spectacular and bewildering; it is clear that reappraisal of our ideas on its pharmacology is essential. The view that its action is confined to the central nervous system requires revision now that outstanding metabolic actions, which are located at the cellular level, have been clearly established.

References

1. Smith, P. K. 1949. Pharmacol. Rev. **1:** 353.
2. Coburn, A. F. 1943. Bull. Johns Hopkins Hosp. **73:** 435.
3. Reid, J., R. D. Watson & D. H. Sproull. 1950. Quart. J. Med. **19:** 1.
4. Ernstene, A. C. 1930. Am. J. Med. Sci. **180:** 12.
5. Reid, J. & D. H. Sproull. 1957. Brit. Med. J. **1:** 1089.
6. Reid, J. 1957. Scot. Med. J. **2:** 91.
7. Tenney, S. M. & R. M. Miller. 1955. Am. J. Med. **19:** 498.
8. Cochran, J. B. 1952. Brit. Med. J. **2:** 964.
9. Cochran, J. B. 1954. Brit. Med. J. **1:** 733.
10. Sproull, D. H. 1954. Brit. J. Pharmacol. **9:** 262.
11. Alexander, W. D. & K. W. M. Johnson. 1956. Clin. Sci. **15:** 593.
12. Alexander, W. D., A. I. Macdougall, M. F. Oliver & G. S. Boyd. 1959. Clin. Sci. **18:** 195.
13. Ingle, D. J. 1950. Proc. Soc. Exptl. Biol. Med. **75:** 673.
14. Smith, M. J. H., B. W. Meade & J. Bornstein. 1952. Biochem. J. **51:** 18.
15. Reid, J., A. I. Macdougall & M. M. Andrews. 1957. Brit. Med. J. **2:** 1071.
16. Reid, J. & T. D. Lightbody. 1959. Brit. Med. J. **1:** 897.
17. Reid, J. 1948. Quart. J. Med. **17:** 139.

VISCERAL RECEPTORS AND VISCERAL PAIN

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The nonnarcotic drugs (or antalgics of Fourneau), for relief of pain, are used because of their ability to relieve the lesser types or degrees of pain—discomfort, ache, soreness, and suffering—and because they do not have tolerance-inducing and addicting properties. Experience teaches that they do not relieve pain of any greater severity. On the other hand, the narcotic, morphinelike analgesics are superior to the antalgics in that they are able not only to relieve severe pain but also most kinds of aches; they have a sedative quality as well. The difference between the two types of drugs would seem to be principally a quantitative one, but this does not appear to be the case. They differ sufficiently in their actions on the central nervous system to raise the question of whether they might not act at entirely different sites, one blocking pain from within the central nervous system, and the other blocking it from without. For these reasons, the cutaneous and visceral receptors have been studied with particular reference to the stimuli and conditions that evoke pain, the mode of action of analgesics, and the means employed for their evaluation.

Conditions Which Evoke Pain

Cutaneous nociception. Pain is provoked by any form of noxious stimuli, whether mechanical, electric, thermal, or chemical, acting upon cutaneous receptors, whereas the same forms of nociception applied to visceral or most deep structures evoke no such sensation. For instance, it is well known that once one of the major body cavities has been opened under local anesthesia, surgical operations involving excisions, crushing, and cauterization may be performed without causing any sensation of pain (Lennander, 1902 and 1906; Mackenzie, 1909; Lewis, 1942). Certain manipulations such as traction on the mesenteric blood vessels (Forbes, 1928; Alvarez, 1934) and overdistension or spasm of hollow viscera may induce pain. Certain other structures—the periosteum, deep fascia, and the gonadal coverings—give rise to pain when struck, punctured, or severely squeezed (Lennander, 1906; Foerster, 1927; Kellgren, 1937 and 1939). Cutaneous pain is acute and generally of short duration.

Vascular nociception. Puncture of arteries (Bazett and McGlone, 1928; Waterston, 1933) and intra-arterial injection of hypertonic electrolytes in small volume may cause a response varying from an ache to a diffuse pain in man, and an apparent pain reaction or pseudaffective response—vocalization, struggle, and transient hypertension—in animals (Woodworth and Sherrington, 1904). Intravenous injection of the same material is without effect. It has been shown that in man adrenaline vasoconstriction on intra-arterial injection does not cause pain, whereas hypertonic $BaCl_2$ (Frölich and Meyer, 1922) and NaI do (Brooks, 1924; Singleton, 1928). In animals (cats and dogs), lactic acid is as effective as $BaCl_2$ (Burget and Livingston, 1931), and NaI and NaCl are equally effective whether injected into a limb artery or into the hepatic, splenic, or superior mesenteric abdominal arteries (Odermatt, 1922; Moore and Moore, 1932 and 1933; Moore and Singleton, 1933; Moore, 1938). Vascular pain may be taken as a sample of visceral pain in that it is diffuse and tends to persist.

Irritation and vascular change. It is evident that many forms of irritation or physicochemical stimulation may serve as a stimulus to evoke discomfort to the point of pain from visceral receptors. The stimulus may also arise following prolonged ischemia and local anoxia, or following local irritation causing direct or antidromic vasodilatation and inflammation (Lewis, 1927 and 1942; Ungar, 1952; Landau and Bishop, 1953). The influence of such states on the caliber and permeability of blood vessels, and on the diffusion and leakage of plasma or intracellular elements, inorganic as well as organic, seems to be of major importance as a factor that lowers the threshold of the visceral receptors, rendering them more sensitive to their usual or specific stimulus or, possibly, to other forms of stimuli. Whether the same receptors participate in local (visceral) functions at low intensities of stimulation and evoke pain only when the stimuli are adequate or sufficiently intense to fire most of the receptor neurons, including those with collaterals that converge on pain internuncials, or whether local reflexes and pain are mediated by separate visceral receptors, are problems which await experimental solution

Liberated chemical agents. With reference to the role of diffused or liberated substances in the genesis of visceral pain, Bommer (1924) suggested that potassium ions may cause pain, and Häbler and Hummel (1928) and Reimer (1932) have reported potassium concentrations in inflammatory exudates and tissue fluids that are sufficiently high to stimulate the receptors that evoke the pseudaffective response (Moore, 1938; Benjamin, 1959). Lewis's (1924, 1927) H-substance, which is released in hyperalgesic skin following local irritation or by antidromic stimulation of cutaneous nerves and causes pain when injected intradermally, is not histamine, potassium, or acetylcholine. According to Rosenthal (1950), histamine injected intradermally also causes pain. Armstrong *et al.* (1953, 1957) have obtained a pain-producing substance from blister fluid, and also from plasma, inflammatory, pleural, peritoneal, and other such fluids, but only after contact with glass. It thus resembles the Bradykinin polypeptides and, like them, possesses some oxytocic activity. Habgood (1950) has demonstrated the liberation of an H-substance by antidromic stimulation of a cutaneous nerve in frog skin; the H-substance signals its presence by evoking a potential discharge from an adjacent nerve terminal that interdigitates with the nerve being stimulated. Lowenstein (1956) has been able to facilitate the activity of single touch receptors in a toad's skin either by stimulating the sympathetic nerve for the region, or by local or intravascular application of adrenaline or noradrenaline. Another substance, adenosine triphosphate (ATP), has been found to be liberated on antidromic stimulation of a sensory nerve. Holton (1959) has shown that ATP appears in the perfusion fluid after antidromic stimulation of the great auricular nerve in an isolated, perfused rabbit's ear; she suggests that ATP is liberated along with noradrenaline since, according to Schuman (1958), ATP binds noradrenaline in sympathetic nerves. Products of proteolytic breakdown in inflammation and infection may also serve as local irritants (Ungar, 1937 and 1952; Chapman *et al.*, 1959).

Two protective systems? The association of irritation with the release of a sensitizing substance appears to form a general basis, if not a prerequisite, for visceral receptor stimulation that will evoke the sensation of visceral pain with its tendency to diffuseness and durability. In contrast, both the stimulation and the sensation proceed at a much faster tempo in the case of classic cutaneous pain. These differences point to the possibility of two protective systems with largely separate receptors and effectors, one directed primarily at the *milieu externe* with fast nerves and somatic muscles to serve it and the other directed primarily at the *milieu interne*, served by the slower autonomic nerves, plain muscles, and glands.

The Receptors

Specialized receptors. The morphological differences between the receptors for olfaction, vision, hearing and equilibration, taste, and muscle and joint sense provide ample evidence of the need for specific structures for receptor function. The receptors that are assumed to be responsible for the reception of nociceptive stimuli, however, are devoid of any structural organization, and consist simply of free-branching unmyelinated varicose nerve terminals. This view of the nociceptors is based upon the free-branching structure of the sensory terminals in the cornea, which have been considered purely nociceptive in function. Recently, Lele and Weddell (1956), reviving older claims, showed that the corneal receptors are capable of sensing tactile and thermal stimuli, as well as the stimulus of pain. The differentiation of the modalities of corneal sensibilities is entirely dependent upon the central analyzers, which minimizes the necessity for specialization at the periphery.

Somatic triad. In the skin, nociceptors are believed to consist of a similar system of free-branching unmyelinated varicose terminals that arise from the myelinated subepithelial plexus and infiltrate between the epithelial cells after losing their myelin sheaths. The other modalities of cutaneous sensation (heat, cold, touch, and pressure), especially in highly sensitive areas such as the palms, soles, oral, anal, and genital orifices, are served by specialized receptor organs. According to Miller *et al.* (1958), the somatic sensory receptors in different layers and types of skin and in deep fascia and tendons consist of a triad of homologous endings: (1) free-branching terminals without expanded tips; (2) unencapsulated branching fibers with expanded tips (for example, Merkel's disks and Ruffini or Ruffinilike endings); and (3) encapsulated endings (for example, Meissner's corpuscles, Krause's end bulbs, Pacinian corpuscles, and simple bulbs with few lamellae). As the coverings of an encapsulated organ such as the Pacinian corpuscle can be peeled off without destroying the excitability of the nerve fiber core by pressure stimulation (Lowenstein and Rathkamp, 1958), it may be concluded that the encapsulated coverings and cells are not essential for the transducer function of the receptor. This does not exclude the possibility that the coverings may serve to increase the specificity of the receptor for its appropriate stimulus by shielding it from stimulation by nonspecific or less specific stimuli. It is evident that the essential element of the specialized cutaneous receptors is its core of unmyelinated, usually branching, axons derived from myelinated fibers that have shed their myelin sheaths a short distance outside or within the capsule. Each is adapted for the reception of different forms of stimuli and is connected with different pathways to specific central perception circuits or analyzers.

Pain receptors. Since there are two types of neurons that convey pain impulses from the skin to the spinal cord, namely, one with relatively fast myelinated A-delta fibers and the other with slow unmyelinated C fibers (Gasser and Erlanger, 1927 and 1929; Lewis and Pochin, 1937), and since most, if not all, of the cutaneous unmyelinated free-branching terminals are the naked endings of myelinated fibers, fast pain may be regarded as being chiefly of cutaneous origin. The fact that slow pain is commonly evoked in sequence with fast pain on nociceptive stimulation of the skin (Gad and Goldscheider, 1892; von Frey, 1896 and 1922; Thunberg, 1902; Lewis and Pochin, 1937; Lewis, 1942), suggests that the slow nociceptors must be nearby. Furthermore, the cutaneous nerve trunks contain a large proportion of unmyelinated C fibers. Although it is not possible to distinguish between the two types of endings as such, it can readily be seen that the adjacent blood vessels contain a plexus of unmyelinated nerves in the adventitia.

Vascular plexus. Although the vascular plexus is stainable by the Ehrlich intravital methylene blue method, it was described by Beale (1860) and Bremer (1882) prior to the introduction of this method. It consists of a network of unmyelinated fibers lying mainly external to the muscle layer, with Remak nuclei along the course of the fibers. It occurs in all blood vessels, being more prominent in arteries than in veins and more dense in the larger than in the smaller vessels. There are fibers in the media as well, but these are fewer and most of them run parallel with the circular plain muscle fibers, without net formation. Some fibers probably extend to the intima. The network appears to be composed of anastomotic fibers, but this does not exclude the interweaving of fibers which are discontinuous and independent. Discontinuity provides for the possibility of intermingling of efferent postganglionic sympathetic fibers with afferent spinal ganglion fibers.* Finding that vascular nerves accompany the smallest arterioles that are without muscle fibers, Kölliker (1862) postulated that they are sensory.

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* There are other ways in which the plexus has been interpreted. A few investigators believe that the plexus is not neural, but is composed of connective tissue cells (Nonidez, 1944; Hinsey, 1929 and 1934). Some look upon the nuclei as belonging to ganglion cells with processes forming synaptic connections, while others regard the plexus as a syncitial net. These conflicting views are reflected in the semantics of this field as follows:

Cajal	1894	Neurones sympathetiques interstitiels	Synaptic† (see FIGURE 3)
Stöhr	1935	Terminal reticulum	Syncitial
Boeke	1938	Plexus sympathetiques fondamentales	Syncitial
Meyling	1953	Autonomic interstitial cells	Anastomotic net synaptic with postganglionic autonomic system
Garven	1955	Autonomic ground plexus	Syncitial
Hillarp	1959	" " "	Synaptic†

† Plexus is considered to be part of the postganglionic autonomic system.

These concepts are not particularly applicable to the vascular plexus, which appears to be the terminal processes of postganglionic efferent and spinal ganglionic afferent neurons. In some subepithelial and submucosal locations, however, there may be need for postulating a peripheral ganglionic system (as a parasympathetic relay, perhaps) but this has no bearing upon sensory mechanisms and pain.

Histological evidence for vascular receptors. Vascular receptors stained by intravital methylene blue have been depicted as sprays or clusters of expanded terminals in several locations: in the coronary artery by Dogiel (1898), in the aorta and pulmonary artery by Dogiel's pupil Schemetkin and, more recently, in the walls of many vessels (coronary, pulmonary, aorta and some of its branches, hepatic, gastric, intestinal arteries of guinea pig, cat, and dog) by Niculescu (1958). Dogiel has also depicted a plexus, *das perivasculäre Nervengeflecht*, which he believed to be the *Endungen motorischer Sympatheticus Fasern.* Niculescu has one drawing of a plexus in a thyroid artery. Only the plexiform ending is illustrated in Meyling's (1953) drawings, and in Hillarp's (1959) and Arthur and Shelly's (1959) photographs. L. H. Bogdanove, F. F. Rhodes, and I have been able to photograph the methylene-blue-stained vascular plexus in the iliac (FIGURES 3 and 4), femoral (FIGURE 5), pedal, auricular, gastric (FIGURE 1), intestinal (FIGURE 2), and renal vessels of rats, but we have not seen any of the spray or cluster receptors of Dogiel and Niculescu. We once saw what appeared to be a spray-type receptor on the wall of a gastric vein, but considered that this might be an artifact (FIGURE 1*a*).

Physiological evidence for vascular receptors. Vascular receptors that take part in the reflex regulation of systemic blood pressure, cardiac activity, and respiration are known to be present in the walls of the carotid sinus (Hering, 1924 and 1927; de Castro, 1926 and 1928; Heymans, 1929; Heymans *et al.*, 1933), the aortic arch (de Cyon and Ludwig, 1866; Schmidt and Comroe, 1940), and the pulmonary artery (Whitteridge, 1948).

The existence of receptors in abdominal and limb vessels, first postulated by Latschenberger and Deahna (1876), has been rendered plausible by the influence of pressure changes and chemical agents on perfused hind limbs (Pagano, 1900; Mattheis *et al.*, 1956) and intestine and spleen (Chernigovski, 1940; Osadchy, 1956; Mattheis *et al.*, 1956) isolated from the general circulation, but left in continuity with the nervous system. Thus the addition of acetylcholine, KCl, and CO_2 to the perfusion fluid, or the production of anoxia or acidosis, bring about reflex hypertension that is blocked by Novocain. The acetylcholine effects are abolished by atropine or nicotine, reduced by tetraethylammonium, and markedly sensitized or potentiated by adrenaline or noradrenaline (Mattheis *et al.*, 1956). Brown and Gray (1948) and Douglas and Gray (1953) have recorded the centripetal discharges in the nerves supplying the area following intra-arterial injections of acetylcholine, nicotine, and α-lobeline. The acetylcholine effects are abolished by atropine, hexamethonium, and *d*-tubocurarine, although the block established by the latter two does not interfere with mechanical stimulation, a situation similar to that found by Douglas (1951, 1952) in the glomus caroticum.

These observations suggest that the receptors that are activated by physical and chemical intra-arterial stimuli to evoke vascular responses are probably situated close to the blood vessels, that is, in the adventitial vascular plexus. Although, as Bayliss (1923) has pointed out, "It is difficult here to exclude action on nerve endings outside the blood vessels," there appear to be no other free-branching unmyelinated fiber terminals as near or as abundantly present as the vascular plexus.

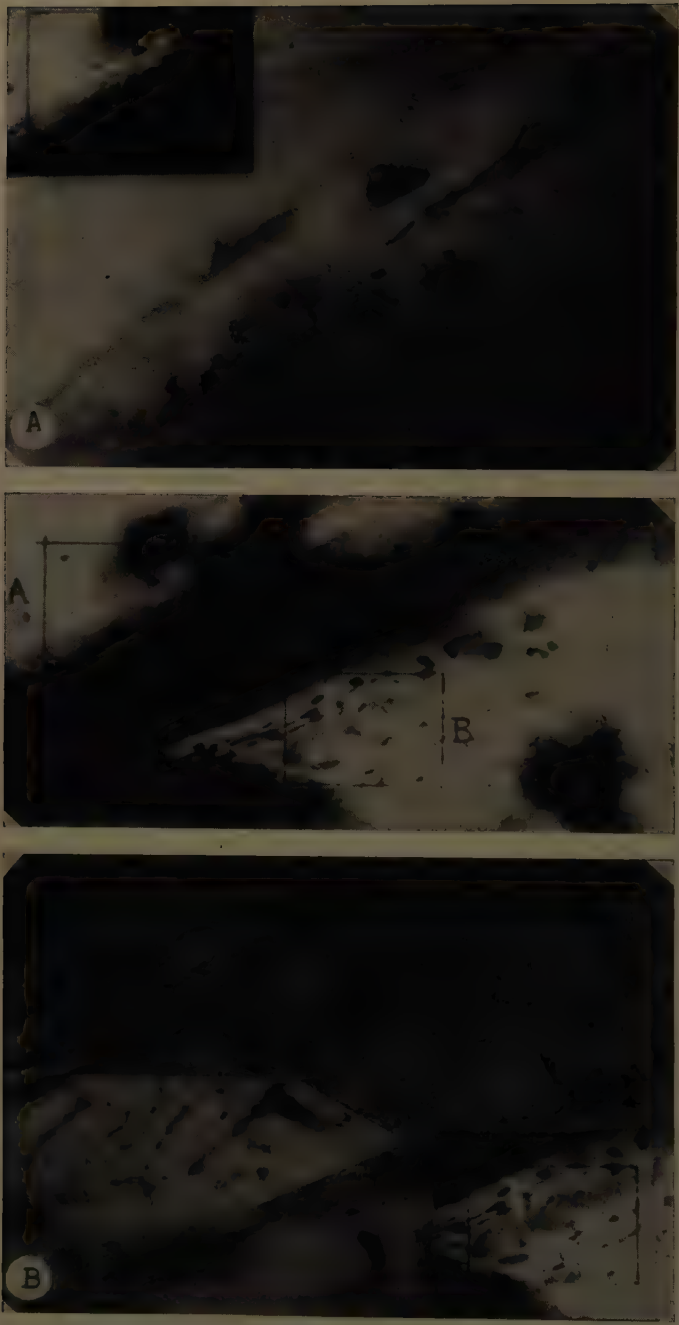

FIGURE 1. Photographs of vein and arteriole in submucosa of rat's stomach, showing location of *A* and *B*. Methylene blue. ×193. (*A*) Spray-type receptor ending(?) on vein. ×870. (*B*) Vascular plexus in arteriole; note varicose fibers and presence of nuclei in the network of fibers. ×870. The darkly stained cells alongside the vessels are mast cells.

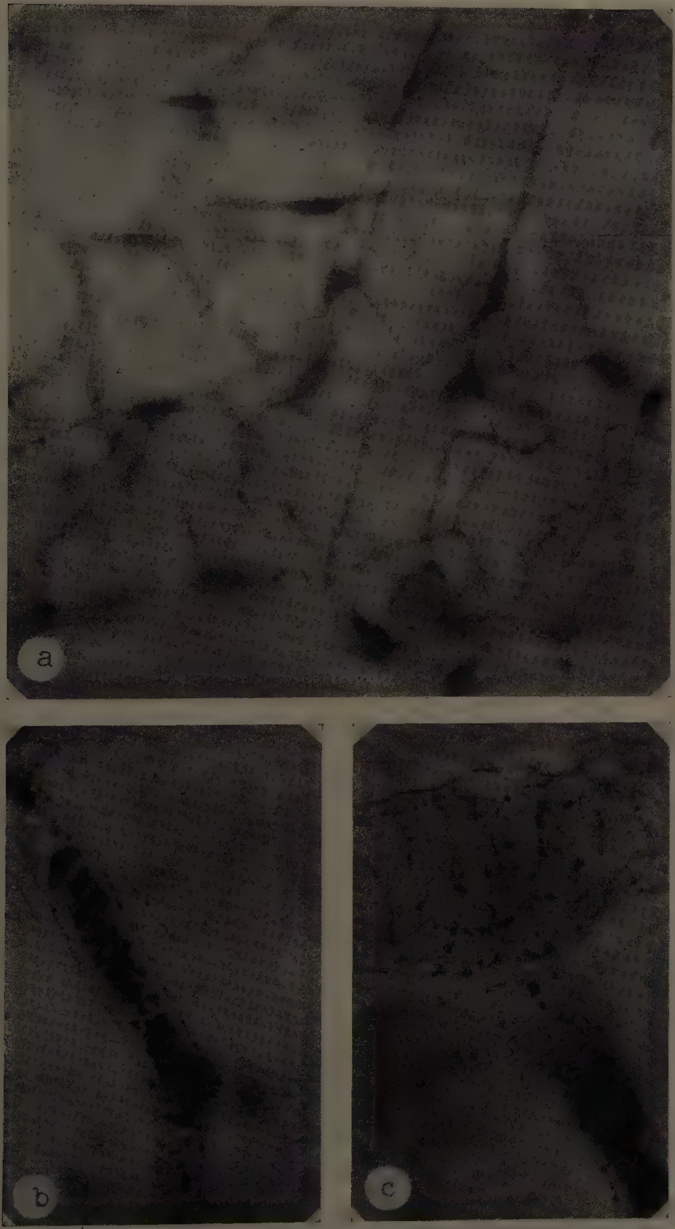

FIGURE 2. Photographs of vascular plexus in different sizes of arterioles. Methylene blue. (*a*) Arteriole in submucosa of rat's stomach. ×847. (*b* and *c*) Arterioles in submucosa of rat's jejunum. ×282.

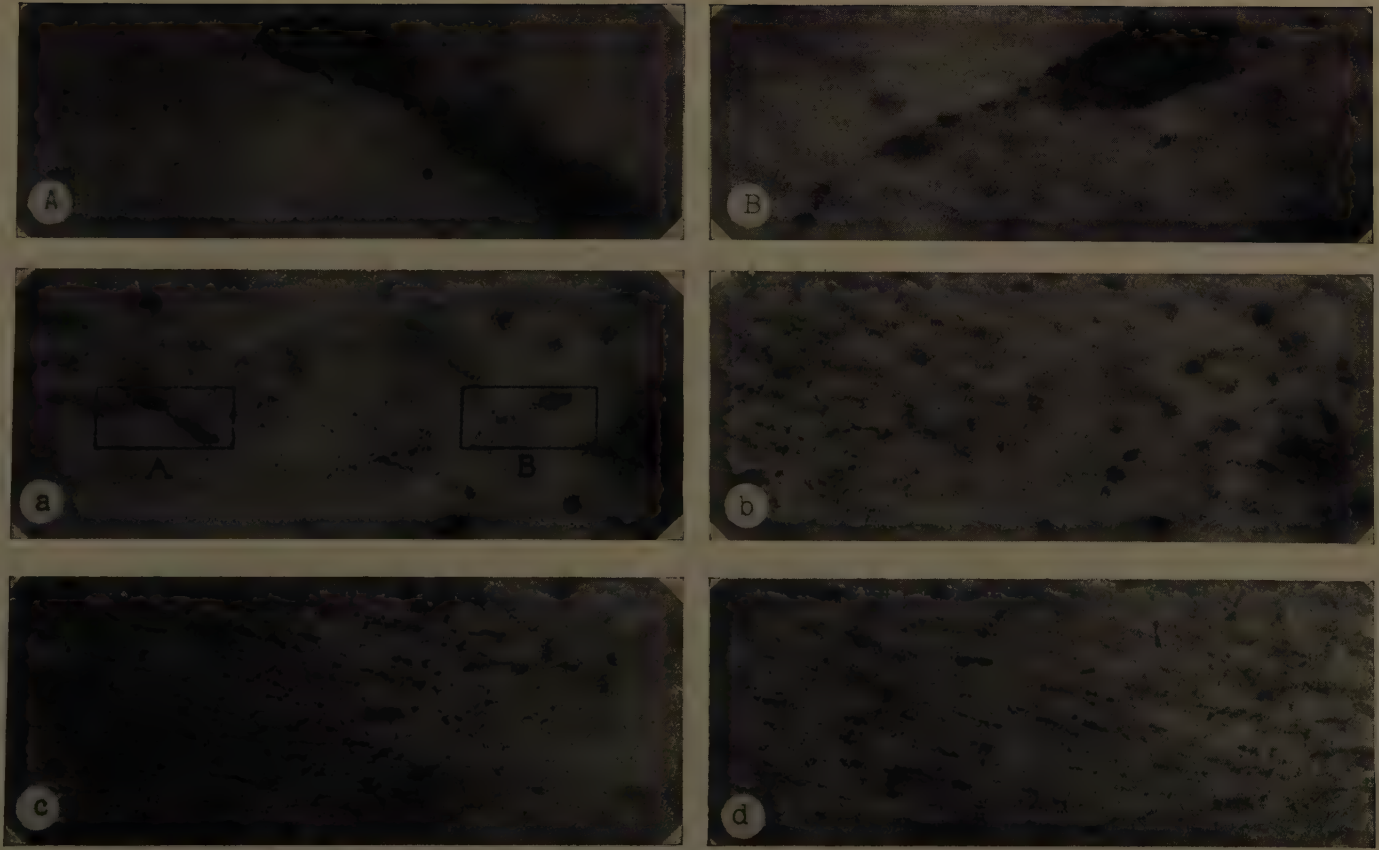

FIGURE 3. Photographs of vascular plexus in adventitia of rat's iliac artery shown in four focal planes, *a* through *d*. Methylene blue. (*A*, *B*) Cajal interstitial cells seen in *a*. Note granules and nuclei stained with methylene blue. ×947. (*a*) Outermost plane showing the location of the Cajal interstitial cells shown in *A* and *B*. Vascular plexus not yet visible. ×260. (*b* through *d*) Vascular plexus at different focal planes.

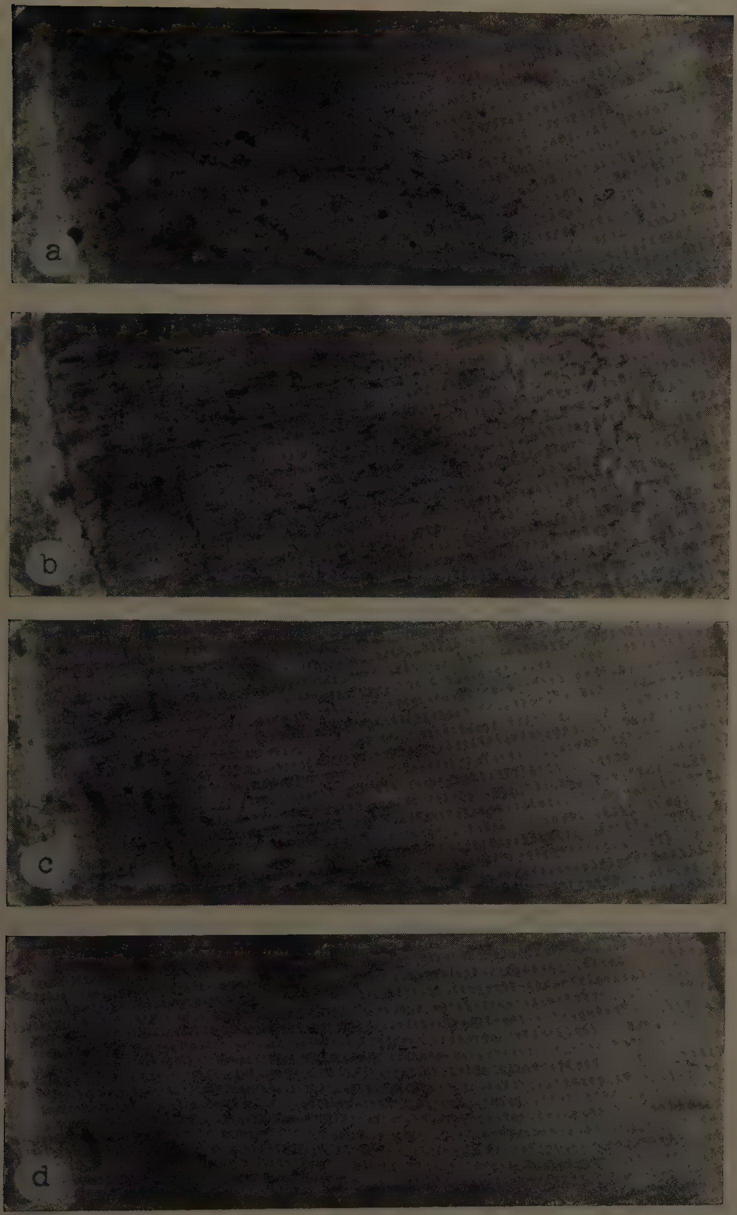

Figure 4. Photographs of vascular plexus in adventitia of rat's iliac artery, shown in four focal planes, *a* through *d*. Methylene blue. ×168. (*a*) Outermost plane showing myelinated and unmyelinated nerve fibers ending in the vessel. (*b*) Vascular plexus on near side of vessel; muscle layer seen as transverse shadows. (*c*) Muscle layer in focus; vascular plexus not visible. (*d*) Vascular plexus again seen on far side of vessel through the other side of the muscle layer.

Visceral pain. The vascular plexus is distributed ubiquitously throughout the body and is well situated to accommodate receptors, not only for local regulation of visceral function, but also for sensing visceral disturbance and pain. In the skin, as elsewhere, there is little evidence that any unmyelinated, free-branching receptors are connected with slow unmyelinated C fiber stems, unless the vascular plexus is taken as such. In spite of this, it is probable that not all the cutaneous receptors are connected with fast myelinated A-

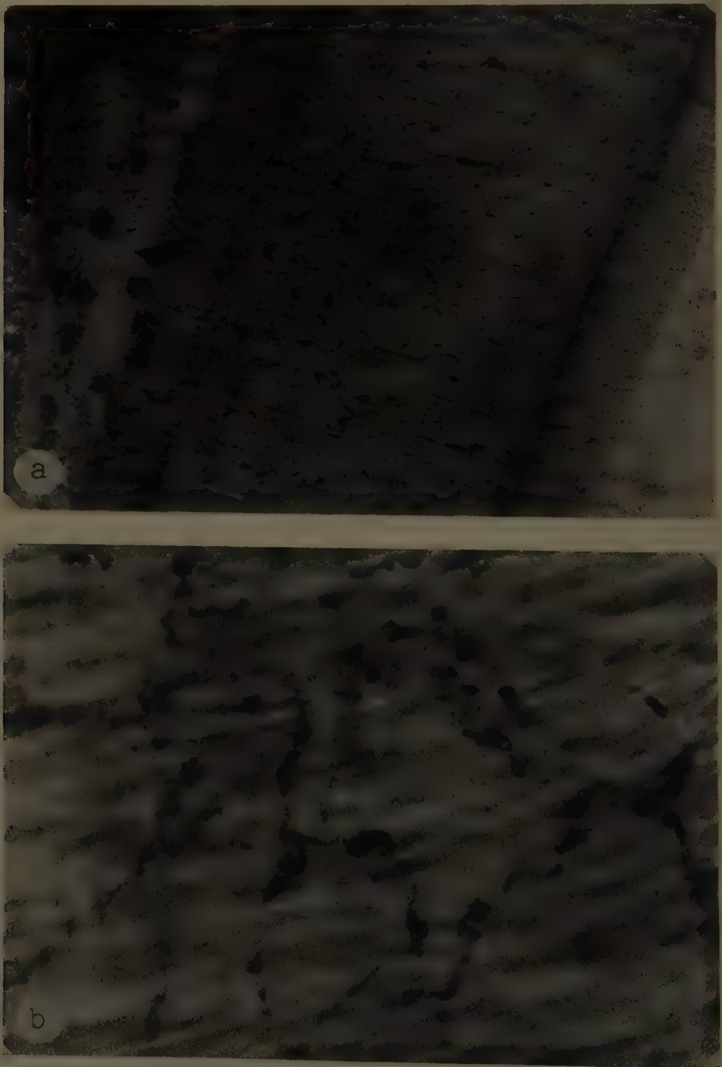

FIGURE 5. Photographs of vascular plexus in rat's femoral artery. Methylene blue. (*a*) Low-power view. Note margins of vessel outlined by the thickness of the muscle layer. ×197. (*b*) High-power view showing the presence of nuclei along the fibers of the vascular plexus. ×986.

delta fibers, since Iggo (1958) has reported that some of the mechanoreceptors and heat and cold receptors in the skin of the cat's leg are innervated by C fibers, which conduct at less than 2 meters/sec. While few unmyelinated, free-branching terminals other than the vascular plexus occur in the subcutaneous, fascial, and other internal connective tissue planes or in deep tissues in general, it is possible that the unmyelinated accessory fibers found in association with the special receptors in encapsulated end organs, muscle spindles, tendons, and fascial attachments of muscle to bone may function as pain fibers (Lavrenko, 1938; Woollard *et al.*, 1940; White and Sweet, 1955). Thus it is probable that both fast and slow pain receptors are present in visceral or deep areas as well as in cutaneous areas, and that the difference between visceral and cutaneous pain is the preponderance of slow pain in visceral and of fast pain in cutaneous injury. The difference will tend to disappear with the severity and duration of the injury, and the corresponding degree of inflammation that develops.

Central Mechanisms Involved in the Reaction to Pain

Afferent input. A number of observations have been made to determine the route of entry to the spinal cord of the afferents from limb and abdominal vessels. Section of the appropriate posterior roots abolishes the pseudaffective response to intra-arterial injection of hypertonic solutions into a limb artery, while section of the artery or of the sympathetic chain does not do so (Dennig, 1924 and 1925; Brjussowa and Lebedenko, 1929; Burget and Livingston, 1931; Moore and Singleton, 1933). Failure on the part of Friedrich (1924), Schilf and Stahl (1925), and Abrashanov (1927) to eliminate the pseudaffective response after sectioning the main nerve trunks (femoral and sciatic) is probably due to incomplete severance of the afferent nerves concerned. On repeating some of the above experiments, C. Braun, F. Guzman, and I found that the pseudaffective response to hypertonic injections into the femoral artery of chloralose dogs is not abolished when the soft tissues—skin, muscle, fascia, nerves, and vessels, except for the femoral vessels and the sciatic nerve—are cut down to the bone at the lower third of the thigh where the injections are made (FIGURE 6, B3). If, however, the sciatic nerve is then divided, vocalization, struggle, and hypertension fail to appear (FIGURE 6, B4). Furthermore, we found that the pseudaffective response to hypertonic injections is not materially affected by removing the skin from the leg distal to the site of injection, thus proving that cutaneous nociceptors are not essential for the response (FIGURE 6, A2). Moore and Singleton (1933) demonstrated that cutting the greater splanchnic nerves and the sympathetic chains prevents the response to intra-arterial injections into the abdominal arteries. The abdominal afferents have no way to reach the spinal cord other than the route taken by the efferent sympathetic. The receptors concerned, as in the case of the skinned leg, are obviously not cutaneous nociceptors. In both cases vascular rather than tissue receptors are probably stimulated.

Chen *et al.* (1937) have shown that all the sympathetic components of the pseudaffective response to stimulation of the sciatic afferents are abolished by section of both dorsal quadrants of the spinal cord in decerebrate cats and dogs, indicating that the ascending pathway is bilateral and confined chiefly to the dorsal half of the cord. The first relay for the pseudaffective response, whether of fast or slow pain, is presumably composed of spinal ganglion neurons with fibers ending in the vicinity of the posterior horn. (It would be interesting to know whether there is an afferent C neuron with completely unmyelinated axons corresponding to the autonomic postganglionic efferent neuron, with the cell body situated within the spinal ganglion or without; or whether all C neurons are a variety of A-delta neurons without myelin sheaths throughout the greater part of its axons.)

Reflex and affective components. Since intra-arterial injections of hypertonic solutions into the abdominal and limb arteries can evoke the pseudaffective response, it is evident that some of their central connections are similar. In fact, the response to direct stimulation of cutaneous nociceptors in the same limb differs from that to intra-arterial injections chiefly in the relative prominence of the flexion and withdrawal response to the local nociception. It is well known (Sherrington, 1906) that flexion is the basic segmental somatic response to nociception and that, as the stimulus is intensified or repeated, recruitment extends the response to other segments and to the autonomic nervous system, bringing about struggling, vocalization, and hypertension. In the case of arterial stimulation, hypertension begins before vocalization and struggling (at least in the chloralose dog), as a pressor effect is the basic visceral response to "fibres whose stimulation results in a reflex rise of blood pressure. Such rise of pressure appears to be associated with the stimulation of nerve fibres whose expression would be that of pain in the un-anesthetized animal" (Bayliss, 1923). The vocalization and struggling are recruited when the intensity of stimulation is adequate. Carroll and Lim (1958, 1960) found that the vocalization response to nociception in the rat consists partly of a reflex vagal response that occurs during nociceptive stimulation and partly of a vocalization afterdischarge which occurs following cessation of nociception. The latter disappears after transections through and caudal to the thalamus, but not rostral to it.

In the conscious animal, the pseudaffective response is thus the reflex com-

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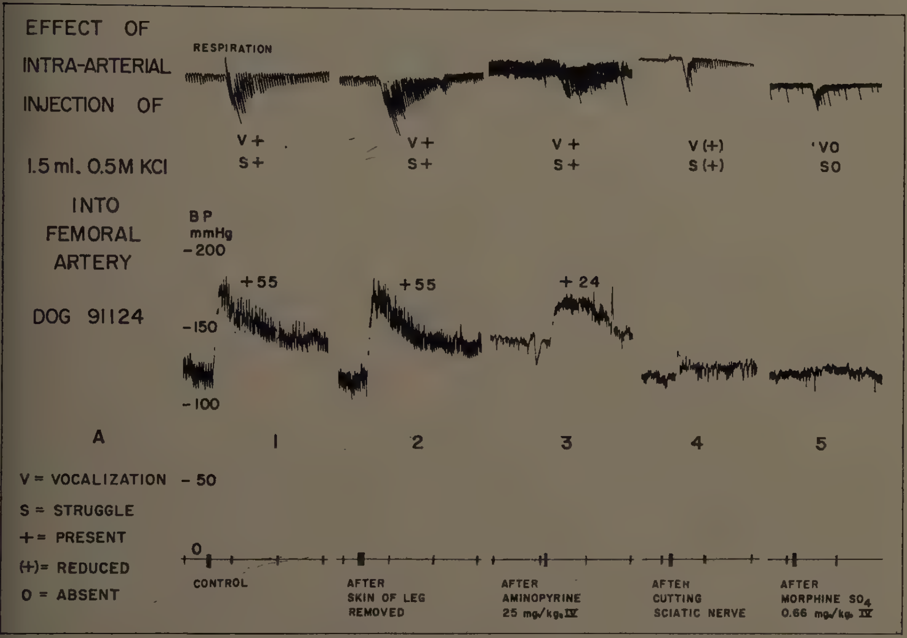
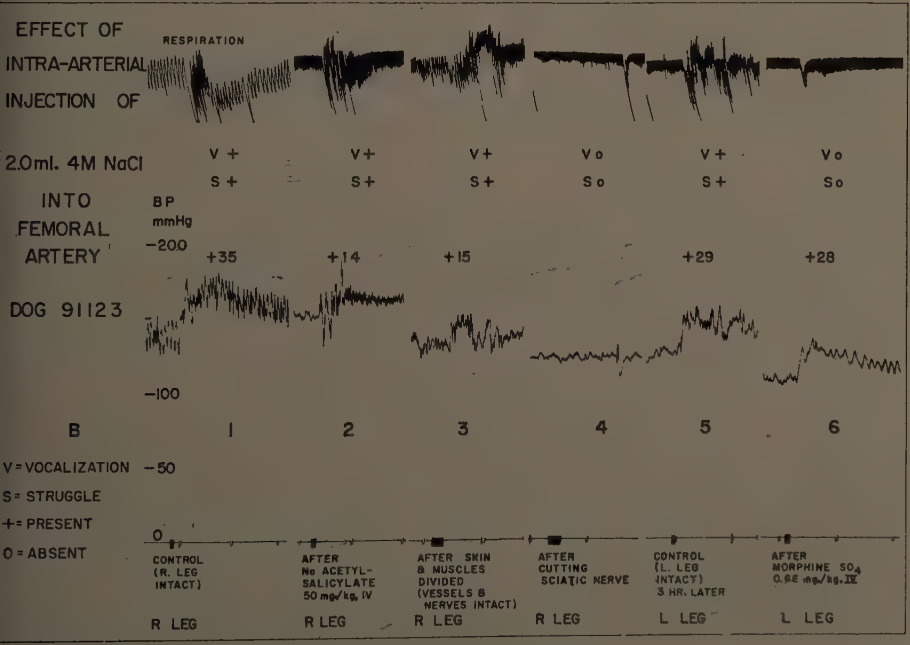
FIGURE 6. Tracings of the pseudaffective response to intra-arterial injections of hypertonic solutions into the femoral artery of the chloralose dog.

A. (1) Control. Pseudaffective response (hypertension, vocalization, and struggle) to intra-arterial injection of 1.5 ml. 0.5 M KCl. (2) After removal of the skin of the leg. Note that the pseudaffective response to intra-arterial injection is unchanged. (3) After aminopyrine (25 mg./kg. I.V.). The hypertensive response is blunted, but vocalization and struggle remain. (4) After cutting the sciatic and saphenous nerves at the level of the arterial injection (lower third of thigh), the hypertensive response is abolished, but vocalization and struggle remain. (5) After morphine sulfate (0.66 mg./kg. I.V.), vocalization and struggle are also abolished.

B. (1) Control. Pseudaffective response to injection of 2.0 ml. 4 M NaCl into the right femoral artery. (2) After Na-acetylsalicylate (50 mg./kg. I.V.), the hypertensive response is reduced, but vocalization and struggle are as evident as before. (3) After circular incision cutting skin and muscle to the bone at the lower third of the thigh, and leaving the femoral vessels and sciatic nerve intact, hypertension to intra-arterial injection remains reduced, and vocalization and struggle are still present. (4) After cutting the sciatic nerve, the pseudaffective response to intra-arterial injection of salt in the right leg is abolished. (5) Control. Pseudaffective response to injection of 2.0 ml. 4 M NaCl into the left femoral artery. (6) After morphine sulfate (0.66 mg./kg. I.V.). Vocalization and struggle against intra-arterial salt injection are abolished, but the hypertensive response remains.

PSEUDAFFECTIVE RESPONSE





ponent of the total reactions to pain, with somatic effectors leading the response associated with fast pain when the cutaneous nociceptors are stimulated, and with autonomic effectors leading the response associated with slow pain when vascular receptors are stimulated. The central "emotional" component includes the afterdischarge and is dependent upon the perception of pain and motivated by the affect generated. Both fast and slow pain produce varying compositions of affect and, while it seems unlikely that each modality of pain is served by specific fast and slow relays, central conduction times indicate that C fibers are involved. The possibility that slow pain may be mediated by convergence of collaterals from C-type vascular afferents on pain internuncials in the brain stem needs to be tested. From the pharmacological standpoint, the importance of the difference between cutaneous (chiefly fast) and visceral (chiefly slow) pain lies not only in the sequence or the duration of events, but also in the nature of the effectors and receptors involved.

Pharmacological applications. Morphine and the narcotic analgesics block the vocalization afterdischarge in rats following cutaneous nociception at a lower dose than vocalization during stimulation. From this it is inferred that morphine blocks the thalamic relays of the pain pathways before it does the vagal (myelencephalic) and the spinal relays. With higher doses, all the other components of the response (vocalization during stimulation, flexion, and struggle) are suppressed. None of the antalgics blocks the response to cutaneous nociception, however induced (see Beecher, 1956 and 1957).

In tests using hypertonic solutions for intra-arterial injections in dogs, my associates and I found that 0.66 mg./kg. of morphine sulfate injected intravenously blocks part of the pseudaffective response, namely vocalization and struggle, but not hypertension. The antalgics Na-acetylsalicylate and aminopyrine, at 50 and 25 mg./kg. intravenously, respectively, have no influence on vocalization and struggle, but seem to produce some blunting of the hypertensive effect (FIGURE 6). It thus appears unlikely that the antalgics act centrally at the dose levels at which they were tested.

On the other hand, use of Randall and Selitto's (1957) pressure test on the yeast-inflamed feet of rats demonstrated that both the morphinelike analgesics and the antalgics raise the threshold to pressure and thus block the response to pressures within this range. Accompanying the antipressalgesia effect is a reduction in local temperature without change in edema and swelling. These observations are followed for 6 to 7 hours after the injection of yeast, and for 3 to 4 hours after drug administration.

When the sciatic and femoral nerves are divided high in the thigh prior to the injection of yeast, the local temperature rises 3 to 4° C. and may rise a little more after yeast. Morphine has no effect on the local temperature in the denervated inflamed foot, but continues to lower the temperature in the innervated inflamed foot, while Na-acetylsalicylate reduces the local temperature of both the innervated and the denervated inflamed foot. Since the morphine effect is seen on the innervated side only, it is evidently produced by central vasoconstriction and, by the same token, the Na-acetylsalicylate effect must be attributed to a local or peripheral action.

The reduction in temperature indicates that a corresponding reduction in congestion and blood flow has taken place, resulting in a change in sensitivity of the visceral receptors, which are assumed to be part of the vascular plexus in the vessel wall. The reversal of some of the inflammatory changes induced by yeast suffices to raise the threshold of excitation to a degree that renders the operating stimuli ineffective. If antalgics relieve pain in this manner by preventing stimulation, the analgesia is no less real in spite of its peripheral origin.

Summary

1. The ubiquity of blood vessels and the presence of a plexus of unmyelinated fibers in the adventitia of all blood vessels, particularly the smaller arteries, suggest that the vascular plexus may contain afferent as well as efferent terminals. The presence of florescent free endings in blood vessels, described by several workers, has not been confirmed, but the abundance of the fiber network in the vascular plexus in the adventitia, as compared with the fibers present in the media, renders such endings unnecessary.

2. The possibility of inducing vascular reflexes from abdominal and limb vessels, as well as from the more specialized sinus, aortic, and cardiopulmonary areas, by physical and chemical stimuli applied to the interior of the blood vessels indicates that vascular receptors are probably widely distributed.

3. The response to intra-arterial stimulation (by injection of hypertonic solutions or chemicals) takes the same form as Sherrington's pseudaffective response to cutaneous nociception, and consists of the following main features: hypertension, vocalization, and struggling.

4. By associating fast pain with the free-branching terminals in the skin derived from A-delta fibers and slow pain with the C fiber branching or network system in blood vessels, it is possible to regard cutaneous pain as mediated chiefly by the fast receptors, and visceral pain, in areas which are usually relatively insensitive, as mediated chiefly by the slow receptors in the vascular plexus.

5. It is pointed out that the nonnarcotic antalgics do not block cutaneous pain centrally like the narcotic analgesics. The former probably relieve visceral pain by a peripheral action that depends upon antagonizing or reducing the condition that favors stimulation of visceral or slow pain receptors in blood vessels. The futility of evaluating nonnarcotic antalgics by using methods employing cutaneous nociception is obvious.

References

ABRASHANOV, A. A. 1927. Arch. klin. Chir. Langenbecks. **146:** 420.

ALVAREZ, W. C. 1934. J. Am. Med. Assoc. **102:** 1351.

ARMSTRONG, D., R. M. L. DRY, C. A. KEELE & J. W. MARKHAM. 1953. J. Physiol. London **120:** 326.

ARMSTRONG, D., J. B. JEPSON, C. A. KEELE & J. W. STEWART. 1957. J. Physiol. London. **135:** 350.

ARTHUR, R. P. & W. B. SHELLEY. 1959. J. Invest. Dermatol. **33:** 121.

BAYLISS, W. M. 1923. The Vasomotor System. Longmans, Green. London, England.

BAZETT, H. C. & B. MCGLONE. 1928. Brain. **51:** 18.

BEALE, L. S. 1860. Proc. Roy. Soc. London. **10:** 519.

BEECHER, H. K. 1956. J. Chronic Diseases. **4:** 11.

BEECHER, H. K. 1957. Pharmacol. Rev. **9:** 59.

Benjamin, F. B. 1959. Federation Proc. **18:** 33.
Boeke, J. 1938. Anat. Anz. **86:** 150.
Bommer, S. 1924. Klin. Wochschr. **3:** 1758.
Bremer, L. 1882. Arch. mikroskop. Anat. Entwicklungsmech. **21:** 663.
Brooks, B. 1924. J. Am. Med. Assoc. **82:** 1016.
Brown, G. L. & J. A. B. Gray. 1948. J. Physiol. London. **107:** 306.
Brjussowa, S. S. & W. W. Lebedenko. 1929. Z. ges. exptl. Med. **49:** 29.
Burget, G. E. & W. K. Livingston. 1931. Am. J. Physiol. **97:** 249.
Carroll, M. N. & R. K. S. Lim. 1958. J. Pharmacol. Exptl. Therap. **122:** 10A.
Carroll, M. N. & R. K. S. Lim. 1960. Arch. intern. pharmacodynamie. In press.
Chapman, L. F., H. Goodell & H. G. Wolff. 1959. Federation Proc. **18:** 25.
Chen, M. P., R. K. S. Lim, S. C. Wang & C. L. Yi. 1937. Chinese J. Physiol. **11:** 355.
Chernigovski, V. N. 1940. Fiziol. Zhur. S.S.S.R. **29:** 3, 15, 526.
De Castro, F. 1926. Trabajos inst. Cajal invest. biol. Madrid. **24:** 365.
De Castro, F. 1928. Trabajos inst. Cajal invest. biol. Madrid. **25:** 331.
De Cyon, E. & C. Ludwig. 1866. Ber. sächs. Gesellsch. **18:** 307.
Dennig, H. 1924. Klin. Wochschr. **3:** 727.
Dennig, H. 1925. Klin. Wochschr. **4:** 66.
Dogiel, A. S. 1898. Arch. mikroskop. Anat. **52:** 44.
Douglas, W. W. & J. A. B. Gray. 1953. J. Physiol. London. **119:** 118.
Douglas, W. W. 1951. J. Physiol. London. **115:** 705.
Douglas, W. W. 1952. J. Physiol. London. **118:** 373.
Foerster, O. 1927. Die Leitungsbahnen des Schmerzgefühls und die chirurgische Behandlung der Schmerzzustände. Urban u. Schwarzenberg. Berlin, Germany.
Forbes, A. 1928. New Engl. J. Med. **99:** 555.
Frey, M. von 1896. Abhandl. math. naturw. Kl. sächs. Akad. Wiss. Leipzig. **40:** 175.
Frey, M. von 1922. Z. Biol. **76:** 1.
Friedrich, H. 1924. Klin. Wochschr. **3:** 2035.
Frölich, A. & H. H. Meyer. 1922. Klin. Wochschr. **1:** 1368.
Gad, J. & A. Goldscheider. 1892. Z. klin. Med. **20:** 339.
Garven, H. S. D. 1955. Acta Neuroveget. (Vienna), Suppl. 6.
Gasser, H. S. & J. Erlanger. 1927. Am. J. Physiol. **80:** 22.
Gasser, H. S. & J. Erlanger. 1929. Am. J. Physiol. **88:** 581.
Habgood, J. S. 1950. J. Physiol. London. **111:** 195.
Häbler, C. & R. Hummel. 1928. Klin. Wochschr. **7:** 2151.
Hering, H. E. 1924. Münch. med. Wochschr. **701:** 1265, 1775.
Hering, H. E. 1927. Die Karotissinus reflex auf Herz und Gefässe. Steinkopf. Dresden and Leipzig.
Heymans, C. 1929. Le Sinus Carotidien et les Autres Zones Vasosensibles Réflexogènes. Soc. sci. Bruxelles, Louvain, Belgium.
Heymans, C., J. J. Bouckaert & P. Regniers. 1933. Le Sinus Carotidien et la Zone Homologue Cardio-aortique. Doin. Paris, France.
Hillarp, N.-A. 1959. Acta Physiol. Scand. **46:** Suppl. 157.
Hinsey, J. C. 1929. J. Comp. Neurol. **47:** 23.
Hinsey, J. C. 1934. Physiol. Rev. **14:** 514.
Holton, P. 1959. J. Physiol. London. **145:** 494.
Iggo, A. 1958. J. Physiol. London. **143:** 47P.
Kellgren, J. H. 1937. Clin. Sci. **3:** 175.
Kellgren, J. H. 1939. Clin. Sci. **4:** 35.
Kölliker, A. 1862. Proc. Roy. Soc. London. **12:** 65.
Landau, W. &. G. H. Bishop. 1953. A.M.A. Arch. Neurol. Psychiat. **69:** 490.
Latschenberger, J. & A. Deahna. 1876. Arch. ges. Physiol. Pflüger's. **12:** 157.
Lavrenko, V. V. 1938. Byull. Eksptl. Biol. Med. **5:** 37.
Lele, P. P. & G. Weddell. 1956. Brain. **79:** 119.
Lennander, K. G. 1902. Mitt. Grenzg. Med. Chir. **10:** 38.
Lennander, K. G. 1906. Mitt. Grenzg. Med. Chir. **15:** 465.
Lewis, T. 1924. Heart. **11:** 109.
Lewis, T. 1927. The Blood Vessels of the Human Skin and Their Responses. Shaw. London, England.
Lewis, T. &. E. E. Pochin. 1937. Clin. Sci. **3:** 67.
Lewis, T. 1942. Pain. Macmillan. New York, N.Y.
Lowenstein, W. R. 1956. J. Physiol. London. **132:** 40.
Lowenstein, W. R. & R. Rathkamp. 1958. Science. **127:** 341, 3294.
Mackenzie, J. 1909. Symptoms and Their Interpretation. Shaw. London, England.
Mattheis, H., B. Wiegershausen, G. Otto & G. Scholz. 1956. Arch. exptl. Pathol. Pharmakol. Naunyn-Schmiedeberg's. **229:** 544.

Meyling, H. A. 1953. J. Comp. Neurol. **99:** 495.

Miller, M. R., H. J. Ralston, III & M. Kasahara. 1958. Am. J. Anat. **102:** 183.

Moore, R. M. 1938. Surgery. **3:** 534.

Moore, R. M. & R. E. Moore. 1932. Proc. Soc. Exptl. Biol. Med. **29:** 919.

Moore, R. M. & R. E. Moore. 1933. Am. J. Physiol. **104:** 259.

Moore, R. M. & A. O. Singleton. 1933. Am. J. Physiol. **104:** 267.

Niculescu, I. 1958. Atlas Concerning Morphological Aspects of Visceral Nerve Endings. A Contribution to the Study of the Problem of Interoceptors. Editura Medicala. Bucharest, Romania.

Nonidez, J. F. 1944. Biol. Rev. **19:** 30.

Odermatt, W. 1922. Bruns' Beitr. klin. Chir. **127:** 1.

Osadchy, L. I. 1956. Byull. Eksptl. Biol. Med. **41:** 4.

Pagano, G. 1900. Arch. ital. Biol. **33:** 1.

Ramon y Cajal, S. 1894. Histologie du Systeme Nerveux de l'Homme et des Vertébrés. Inst. Ramon y Cajal. Madrid. Transl. by L. A. Azoulay. 1955. **2:** 923.

Randall, L. O. & J. J. Selitto. 1957. Arch. intern. pharmacodynamie. **111:** 409.

Reimer, C. 1932. Deut. Z. Chir. **236:** 60.

Rosenthal, S. R. 1950. Proc. Soc. Exptl. Biol. Med. **74:** 167.

Schilf, E. &. R. Stahl. 1925. Klin. Wochschr. **4:** 1390.

Schmidt, C. F. & J. H. Comroe. 1940. Physiol. Rev. **20:** 115.

Schuman, H. J. 1958. Arch. exptl. Pathol. Pharmakol. Naunyn-Schmiedeberg's. **233:** 296.

Sherrington, C. S. 1906. The Integrative Action of the Nervous System. Constable. London, England.

Singleton, A. O. 1928. Arch. Surg. **16:** 1232.

Thunberg, T. 1902. Skand. Arch. Physiol. **12:** 394.

Ungar, G. 1937. Congr. Assoc. Physiol. : 297.

Ungar, G. 1952. Lancet. **263:** 742.

Waterston, D. 1933. J. Physiol. London. **77:** 251.

White, J. C. & W. H. Sweet. 1955. Pain: Its Mechanisms and Neurosurgical Control. Thomas. Springfield, Ill.

Whitteridge, D. 1948. J. Physiol. London. **107:** 496.

Woodworth, R. S. & C. S. Sherrington. 1904. J. Physiol. London. **31:** 234.

Woollard, H. H., G. Weddell & J. A. Harpman. 1940. J. Anat. **74:** 413.

THE HISTORY, CHEMISTRY, AND PHARMACOLOGY OF CARISOPRODOL

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Administration of meprobamate to suitable patients produces both tranquilization and muscular relaxation (Berger, 1956). Since elimination of one of these two actions not only could yield new and useful drugs, but might also shed some light on the interrelation between psychic and somatic tension, numerous compounds chemically related to meprobamate (Berger, 1954) were synthesized and subjected to pharmacological evaluation. Of these, N-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate (FIGURE 1), called carisoprodol (Soma, Rela), which differs from meprobamate in having an isopropyl group in place of a hydrogen atom on one of the carbamyl nitrogens, appeared of unusual interest (Berger, 1959). This relatively simple substitution yielded a compound that was surprisingly unlike meprobamate in pharmacological properties (Berger *et al.*, 1959). Carisoprodol not only had an entirely different profile of effects on the central nervous system but, in addition, unexpectedly exhibited analgesic properties of an unusual kind.

Carisoprodol is a bitter, essentially odorless, white crystalline powder. It melts without decomposition at 92° to 94° C. and dissolves in water to the extent of 0.3 mg./ml. at 25° C. and 1.4 mg./ml. at 50° C. It is readily soluble in common organic solvents, but almost insoluble in liquid fats. On boiling with strong acid or alkali, carisoprodol is hydrolyzed to ammonia, isopropylamine, carbon dioxide, and 2-methyl-2-propyl-1,3-propanediol. It is stable in dilute acid and alkali, and is not altered by gastric or intestinal juices at 37° C.

Effect of Carisoprodol on the Central Nervous System

Effect on the electroencephalogram and behavior. The effect of carisoprodol on the electroencephalogram was investigated in unanesthetized cats and rabbits. Cats were anesthetized with ether and bipolar electrodes were placed stereotaxically into various subcortical structures. Needle electrodes were used for cortical recordings. All wound margins were infiltrated with lidocaine, and recordings were begun only after at least one hour had elapsed to allow for elimination of ether. The animals were immobilized with succinylcholine given continuously by intravenous infusion. The drugs, dissolved in 50 per cent propylene glycol, were injected intravenously. In rabbits all surgical procedures were carried out under local anesthesia and the animals were not curarized.

Administration of carisoprodol in doses of 5 to 10 mg./kg. produced a marked decrease in frequency and an increase of amplitude in cortical and subcortical recordings (FIGURE 2). Spindling was seldom seen. Meprobamate in similar doses, in agreement with previously published work, had no effect on the brainwave patterns (Hendley *et al.*, 1954, 1957; Gangloff, 1958, 1959).

Larger doses of carisoprodol caused progressive slowing of frequency and an increase of amplitude until, after a dose of approximately 40 to 60 mg./kg., there

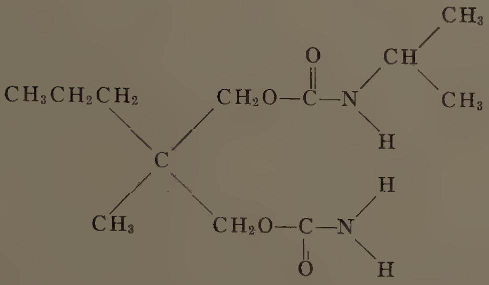

FIGURE 1. The chemical structure of carisoprodol.

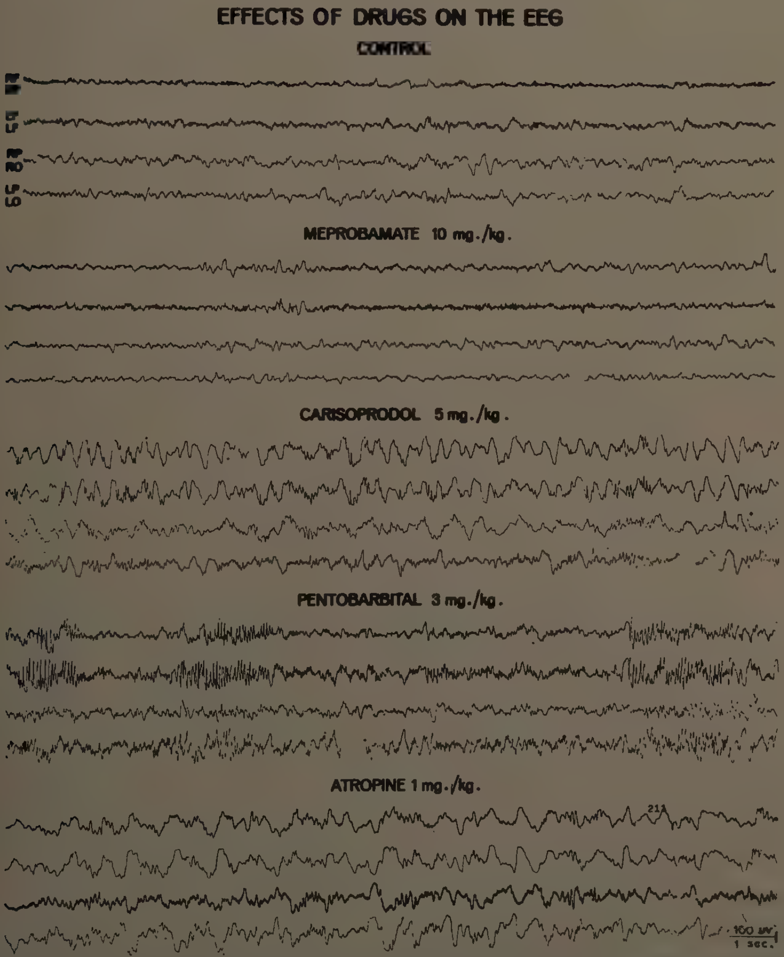

FIGURE 2. Effect of drugs on the electrocorticogram of unanesthetized, uncurarized rabbits. Key: RF, right frontal; RP, right parietal; LF, left frontal; RO, right occipital; LP, left parietal; LO, left occipital.

was obtained an irregular, high-voltage, very low-frequency record interspersed with periods of isoelectricity. Still higher doses were accompanied by greatly reduced activity and longer stretches of electric silence.

Unrestrained and unoperated animals receiving carisoprodol in doses of 5 to 10 mg./kg. usually did not appear drowsy and did not fall asleep. Although carisoprodol in these doses produced marked changes in the electroencephalogram, there were no changes in behavior nor were there any discernible neurological deficits. In this respect carisoprodol resembled atropine, which produces a similar slowing of the brain-wave patterns, as first reported by Wescoe *et al.* (1948), without causing any behavioral changes (Longo, 1956; Bradley and Elkes, 1957). Thus both carisoprodol and atropine show a dissociation between brain-wave responses and behavioral effects. This parallelism holds only as long as these drugs are given in low doses. In larger doses carisoprodol produces muscle relaxation, paralysis and generalized depression of the central nervous system whereas atropine causes excitement.

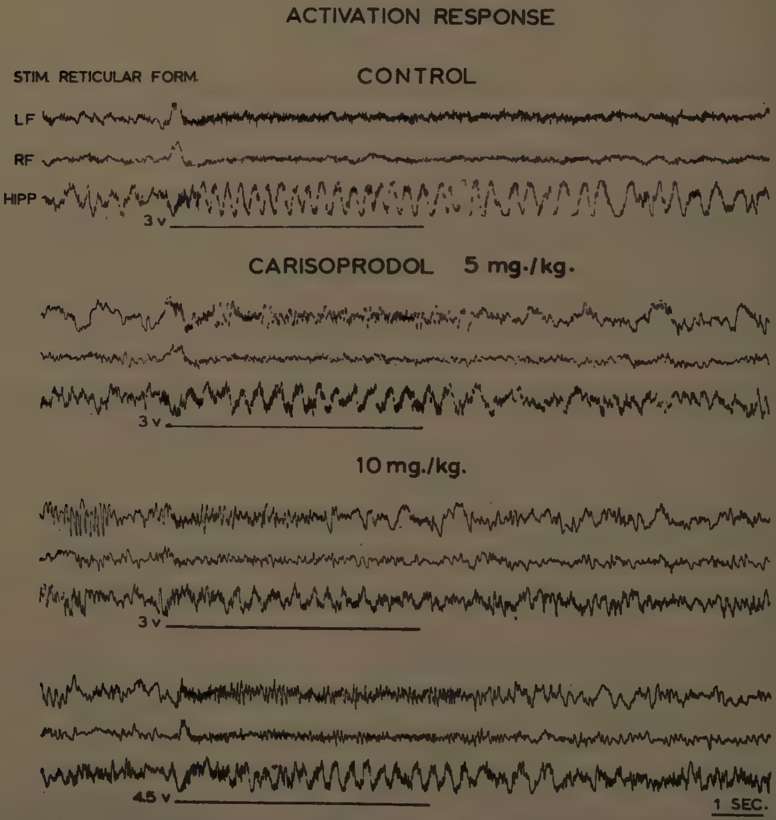

FIGURE 3. Effect of carisoprodol on the activation response produced by the stimulation of the midbrain reticular formation in cats. Solid line indicates the duration of stimulation, 5 sec. at 150 cps. Key: LF, left frontal; RF, right frontal; HIPP, hippocampus.

The brain-wave pattern produced by carisoprodol can be differentiated from that of the barbiturates by the absence of the spindling pattern so characteristic of the latter group of drugs. Another important distinction is discernible from behavioral observations. Animals treated with a barbiturate in a dose sufficient to produce retardation of the brain-wave pattern also show signs of sleepiness.

Effect on arousal. Peripheral stimulation or stimulation of the mesencephalic reticular formation or of the diffuse thalamic system produces a low-voltage, high-frequency electrocorticogram. This arousal or activation response usually outlasts the duration of stimulation. It has been found that carisoprodol in doses of 5 to 10 mg./kg. generally depresses the activation response to both peripheral and central stimulation (FIGURE 3). These effects resemble those produced by atropine, the barbiturates, and other central nervous system depressants. Carisoprodol, like atropine, again shows a dissociation of the electrophysiological arousal phenomena from the behavioral effects. Animals receiving carisoprodol or atropine in doses sufficient to block activation of the electroencephalogram still respond to sensory stimulation and remain alert. On the other hand, animals receiving barbiturates or other sedatives and hypnotics in doses sufficient to obliterate activation of brain-wave patterns appear drowsy and show decreased reactivity to sensory stimuli.

TABLE 1

CONCENTRATIONS OF DRUGS IN μG./ML. REQUIRED TO REDUCE BY 50 PER CENT THE EFFECT OF ACETYLCHOLINE OR HISTAMINE ON THE ISOLATED GUINEA PIG GUT*

	Acetylcholine	Histamine
Carisoprodol	18	48
Meprobamate	55	70
Atropine sulfate	0.002	—
Diphenhydramine HCl	—	0.004

* The drugs remained in contact with the ileum for 2 min. before the spasmogen was added.

Meprobamate in comparable doses differs from carisoprodol and atropine, as well as the sedatives and hypnotics, in affecting neither the electrophysiological arousal responses (Gangloff, 1959) nor the behavioral effects (Berger *et al.*, 1959).

The similarity between the central effects of atropine and carisoprodol made a comparison of their peripheral anticholinergic effects of interest. Carisoprodol did not affect the pupil on local administration and did not reduce salivary secretion produced in mice by intracerebral injection of acetylcholine according to the procedure of Makovsky and Margolin (1954). Although carisoprodol is somewhat more effective than meprobamate in preventing spasm produced by acetylcholine or histamine, it still is an extremely weak antispasmodic when compared to atropine (TABLE 1). In dogs the cardiac retardation and fall of blood pressure produced by stimulation of the peripheral stump of the cut vagus nerve could be inhibited to some extent by administration of carisoprodol in doses of 20 mg./kg. I.V. Similar doses of carisoprodol also reduced by as much as 50 per cent the fall of blood pressure induced by administration of acetylcholine in doses of 25 μg./kg. Carisoprodol in cats did not significantly reduce contractions of the nictitating membrane produced by the stimulation of the superior cervical preganglionic nerve, nor did it affect the carotid sinus pressor reflex in dogs. Thus the peripheral anticholinergic activity of carisoprodol was quite weak. Even under the most favorable circumstances it possessed no more than 1/500 of the anticholinergic activity of atropine.

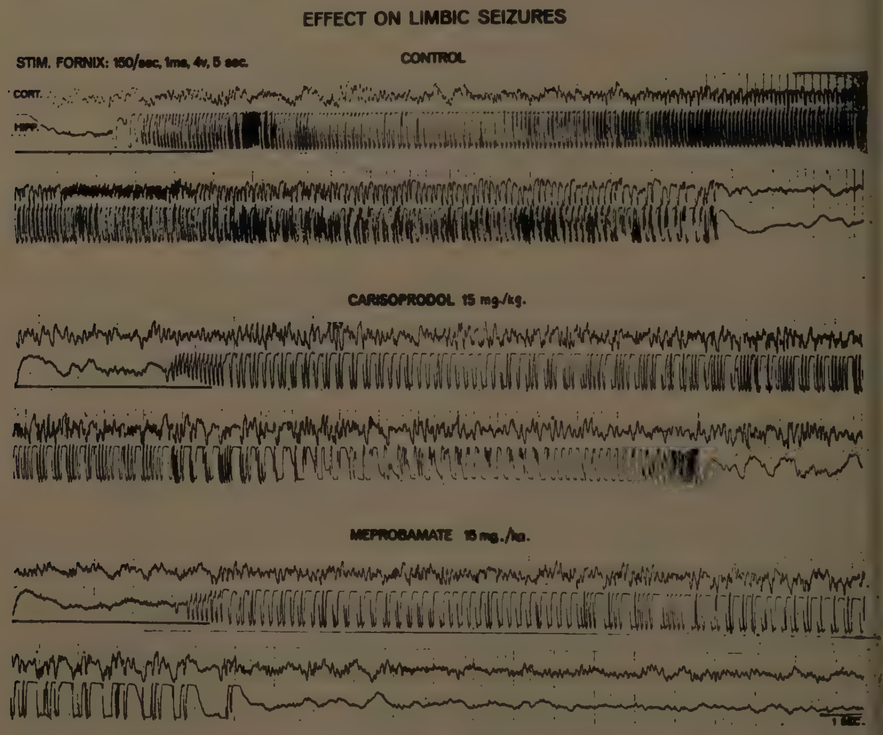

FIGURE 4. Effect of carisoprodol and meprobamate on limbic seizures in unanesthetized, immobilized cats. Stimulus duration, indicated by solid line: seizure duration, control, 36.8 sec.; carisoprodol, 35.6 sec.; meprobamate, 21.5 sec. Key: CORT, cortex; HIPP, hippocampus.

Effect on the limbic system. There are many indications that the limbic system (rhinencephalon) may be intimately associated with emotional activity. Furthermore, all important tranquilizing agents seem to have an effect on the excitability of the limbic system. In view of the chemical similarity between carisoprodol and meprobamate, it appeared of interest to investigate the effect of this new drug upon convulsive discharges set up in the limbic system by electric stimulation.

Electrodes were introduced into the hippocampus and fornix, and seizures were produced by stimulation of the latter structure. The duration of seizures in untreated animals was usually about 30 to 60 sec. These very high-amplitude seizure discharges usually remained confined to the limbic system and did not spread to other subcortical or cortical structures. Meprobamate in relatively low doses sharply attenuated the duration of these seizures (Kletzkin and Berger, 1959). Similar effects have been observed after low doses of barbiturates. On the other hand, carisoprodol had no effect on the duration of these rhinencephalic seizures (FIGURE 4). In this respect carisoprodol again resembles atropine, which also did not decrease or perhaps even slightly enhanced the excitability of the hippocampus. It appears likely that the effectiveness of tranquilizers bears some relation to the action of these drugs on the limbic system (Kletzkin and Berger, 1959). The lack of effect of carisoprodol on the limbic system fits in well with the clinically observed lack of tranquilizing action of this drug.

Comparison of electrophysiological effects of carisoprodol and meprobamate. The differences between the electrophysiological phenomena produced by meprobamate and carisoprodol and certain other drugs are shown in TABLE 2.

TABLE 2
EFFECTS OF DRUGS ON ELECTROPHYSIOLOGICAL PHENOMENA IN UNANESTHETIZED CATS

Compound	Dose (mg./kg.)	Spontaneous cortical activity	Cortical and hippocampal arousal	Limbic seizures	Recruiting
Meprobamate	20	Unaffected	Unaffected	Depressed	Depressed
Carisoprodol	10	Depressed	Depressed	Unaffected	Enhanced
Atropine	1	Depressed	Depressed	Unaffected	Depressed
Pentobarbital	5	Depressed	Depressed	Depressed	Enhanced

This table describes the effect of small doses of these drugs in unanesthetized cats.

The pronounced and unexpected dissimilarity between the neuropharmacological effects of carisoprodol and meprobamate can be noted. Carisoprodol produces many effects that are the reverse of those observed after administration of meprobamate. Carisoprodol increases the amplitude and decreases the frequency of spontaneous electric activity of the cortex and depresses cortical and hippocampal arousal. Meprobamate does not affect these phenomena, but depresses limbic seizures and recruiting that are unaffected or enhanced by carisoprodol.

The neuropharmacological effects produced by carisoprodol are in some respects related to those produced by atropine and the barbiturates. Carisoprodol differs from atropine in being devoid of its peripheral anticholinergic action and in showing central depressant effects in large doses. It differs from pentobarbital in showing a dissociation between the brain-wave and behavioral effects and in being devoid of an action on the limbic system.

The Muscle Relaxant Action

Centrally acting skeletal muscle relaxants can be evaluated objectively according to four pharmacological actions: the paralysis of intact animals, the depression of spinal reflexes, the anticonvulsant effect, and the relief of decerebrate rigidity.

Paralyzing action. Since it is difficult to measure muscle relaxation quantitatively, it has become customary to evaluate the relative activity of centrally acting skeletal muscle relaxants by measuring their paralyzing action. All these agents are capable of producing reversible paralysis of voluntary muscles. Relaxation of skeletal muscles and paralysis result from the action of such drugs on the central nervous system, since stimulation of the sciatic nerve of a paralyzed animal produces prompt contraction of the hind leg muscles. Conduction in the peripheral nerve, transmission at the myoneural junction, and contractability of the skeletal muscles are not significantly affected even in completely paralyzed animals. The pharmacological effect produced by carisoprodol is therefore of the same type as that produced by mephenesin (Berger and Bradley, 1946) and other centrally acting skeletal muscle relaxants (Berger, 1949 and 1952; Marsh, 1955), but differs from that produced by curare and related substances that block transmission at the myoneural junction. The absence of the righting reflex may be taken as a convenient sign of the presence of paralysis, and it affords a definite end point for the measurement of the 50-per cent effective dose. TABLE 3 gives the mean paralyzing and lethal doses of carisoprodol, mephenesin, and meprobamate in mice and rats. In both species carisoprodol is markedly more effective as a muscle relaxant than either of the older compounds. Carisoprodol also possesses a significantly greater margin of safety between the mean effective and mean lethal doses than the other drugs.

TABLE 3

THE PARALYZING AND LETHAL ACTIONS OF MEPHENESIN, MEPROBAMATE, AND CARISOPRODOL IN MICE AND RATS

Species	Compound	PD_{50} (mg./kg. I.P.)	LD_{50} (mg./kg. I.P.)	Safety margin
Mice	Mephenesin	180 ± 10	610 ± 10	3.4
Mice	Meprobamate	235 ± 7	800 ± 15	3.4
Mice	Carisoprodol	165 ± 17	980 ± 78	5.9
Rats	Mephenesin	120 ± 10	430 ± 18	3.6
Rats	Meprobamate	300 ± 16	545 ± 40	1.8
Rats	Carisoprodol	92 ± 13	450 ± 61	4.9

Effect on spinal reflexes. Carisoprodol, like the older centrally acting muscle relaxants (del Castillo, 1948), has a depressant effect on multineuronal reflexes. Like mephenesin or meprobamate, it appears to depress more readily the more complicated reflexes, such as the crossed extensor, than the simple reflexes, such as the flexor reflex. Two-neuron reflexes such as the knee jerk, as a rule, are not affected. Carisoprodol, however, should not be classified with interneuronal blocking agents such as mephenesin or meprobamate because it differs from these centrally acting skeletal muscle relaxants in having a marked blocking effect on the reticular formation.

Anticonvulsant action. Muscle relaxants usually antagonize the convulsant and lethal effects of strychnine (Berger, 1949). Mephenesin is outstanding in this respect, as it is capable, under appropriate conditions, of protecting animals against the convulsant and lethal effects of several LD_{50} doses of strychnine (Berger, 1947). Carisoprodol, however, is a weak strychnine antagonist. When a definitely lethal dose of strychnine (LD_{95}) was given intraperitoneally 30 min. after the administration of graded doses of carisoprodol, it appeared impossible to protect animals from convulsions or death with any amount of the drug. Carisoprodol, however, exerted some effect, as it was able to prolong the time until death and also to modify the character of the convulsions. The relative activities of mephenesin, meprobamate, and carisoprodol in protecting animals from strychnine convulsions or death are given in TABLE 4. It is of interest to note that mephenesin and meprobamate, which are not closely related in chemical structure, share the ability to counteract convulsions and death in similar doses while carisoprodol, which so closely resembles meprobamate chemically, is a very weak strychnine antagonist.

TABLE 4
ANTAGONISTIC EFFECTS OF DRUGS TO STRYCHNINE*

Compound	Mean protective dose (mg./kg.) against	
	Convulsions	Deaths
Mephenesin	485 ± 62	230 ± 29
Meprobamate	470 ± 23	210 ± 28
Carisoprodol	> 980	> 980

* In doses of 2.5 mg./kg. given intraperitoneally to mice 30 min. after intraperitoneal administration of the drugs.

Carisoprodol, however, can protect animals against the convulsive and lethal effects of Metrazol but is, in this respect, only about one half as effective as meprobamate. It is also less potent than meprobamate in abolishing the tonic extensor phase of electroshock seizures in mice.

Effect on decerebrate rigidity. Decerebrate rigidity appears to present a useful experimental condition for the evaluation of centrally acting muscle relaxants. Like many hypertonic states in human beings, it is characterized by continuous spasm predominating in those skeletal muscles, usually the extensor muscles, that normally resist the effects of gravity.

Decerebration was carried out in cats anesthetized with ether by sectioning the midbrain between the colliculi. The electromyogram was recorded with bipolar needle electrodes inserted into the extensor muscles of the fore or hind limbs and amplified and recorded on a Grass electroencephalograph.

Mephenesin, like other centrally acting skeletal muscle relaxants, is known to be quite ineffective in counteracting decerebrate rigidity. About 24 mg./kg. of mephenesin or meprobamate, given intravenously, was required to produce relaxation of decerebrate rigidity. Carisoprodol, on the other hand, completely abolished the spasticity due to decerebrate rigidity in doses of 3 mg./kg. Mephenesin and meprobamate in doses of 3 mg./kg. had no effect on spasticity. These results are illustrated in FIGURE 5, which also shows that the electrocardiogram was not affected by any of these drugs in the doses given. These experiments indicate that carisoprodol is about 8 times as potent as mephenesin or meprobamate in alleviating decerebrate rigidity in cats.

In summary, then, carisoprodol resembles other relaxants in producing reversible paralysis of skeletal muscles and in depressing multineuronal reflexes to a greater extent than it depresses simple ones. Carisoprodol differs from other centrally acting skeletal muscle relaxants in being much more effective in alleviating decerebrate rigidity and in being a poor strychnine antagonist. Thus carisoprodol may have a different mode of action or act at different sites than other centrally acting skeletal muscle relaxants.

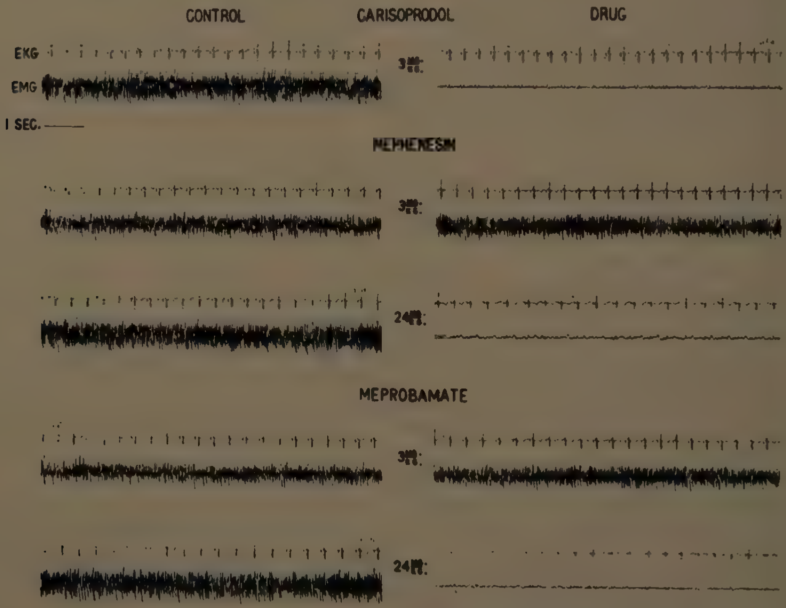

FIGURE 5. The effect of carisoprodol, mephenesin, and meprobamate on the electromyogram (EMG) and electrocardiogram (EKG) of the decerebrate cat.

The Analgesic Action

Most pain-relieving drugs used in medicine belong to one of two major groups: the antipyretic analgesics or the narcotic analgesics. The first group, of which acetylsalicylic acid, phenacetin, antipyrine, and phenylbutazone are typical examples, cannot be evaluated easily in the laboratory. Pharmacologists therefore must use indirect tests, such as antipyretic action or relief of writhing, as signs of the possible analgesic action of these compounds. Narcotic agents such as the opium alkaloids or their synthetic substitutes are evaluated easily in the laboratory by their ability to abolish the natural withdrawal reflexes. The most widely used tests of this type are the hot plate test and the tail flick response to radiant heat. Carisoprodol has been carefully evaluated in a number of procedures that give clear-cut responses with antipyretic or narcotic analgesics. It was found that carisoprodol does not fit into either group of analgesics.

Antipyretic action. The effect of carisoprodol on fever produced by injection of a typhoid-paratyphoid vaccine was investigated in rabbits. The vaccine, diluted 1:10, was given intravenously in an amount of 0.67 mg./kg., and temperatures were recorded on a thermistor thermometer 1 hour before administration of the pyrogen just prior to its injection and at hourly intervals thereafter for 4 or 5 hours. The test drugs were injected intraperitoneally 1 hour after administration of the pyrogen. The effects of these drugs were evaluated by the method of Brownlee (1937, 1939).

Carisoprodol in doses of 200 mg./kg. had a distinct antipyretic action that, however, was weaker than the antipyretic action produced by 100 mg./kg. of acetylsalicylic acid. Carisoprodol in doses of 100 mg./kg. was ineffective as an antipyretic, whereas acetylsalicylic acid in doses of 50 mg./kg. still produced an appreciable antipyretic effect. These results are given in TABLE 5.

TABLE 5
ANTIPYRETIC ACTION OF CARISOPRODOL AND ACETYLSALICYLIC ACID IN RABBITS FEVERED WITH TYPHOID-PARATYPHOID VACCINE

Drug	Dose (mg./kg.)	Number of rabbits	Mean temperature change* (°C.)
Acetylsalicylic acid	200	8	−4.26 ± 1.06
	100	8	−3.66 ± 1.17
	50	8	−0.99 ± 0.43
Carisoprodol	200	8	−2.60 ± 1.17
	100	8	+0.54 ± 0.73
Control	—	17	+1.64 ± 0.47

* The drugs were given intraperitoneally 1 hour after the pyrogen. The mean temperature change is the average of readings taken subsequently at hourly intervals for 3 hours.

Carisoprodol at doses as high as 200 mg./kg. failed to lower the body temperature of normal rabbits.

The writhing test. The analgesic activity of carisoprodol was also evaluated by the phenylquinone-induced writhing reaction described by Siegmund *et al.* (1957). Acetylsalicylic acid and other compounds have been shown to prevent this response. Male albino mice received graded doses of the test drugs intraperitoneally. Thirty minutes later 0.25 ml. of a freshly prepared 0.02 per cent solution of phenylquinone in 5 per cent aqueous ethanol was given to each mouse. Control groups of mice were injected with phenylquinone alone. The mean effective doses were computed according to the method of Miller and Tainter (1944).

Control mice or mice given ineffective compounds usually started writhing about 5 min. after administration of phenylquinone and continued to do so for at least 30 min. Mice were considered protected if they did not show writhing for 30 min. following the injection of phenylquinone.

Acetylsalicylic acid prevented writhing in 50 per cent of mice in doses of 80 ± 9 mg./kg. Carisoprodol had very little effect in this test and did not prevent the occurrence of writhing even when given in doses sufficient to abolish the righting reflex of the animals. The writhing reaction was lost in 50 per cent of mice after doses of 475 ± 41 mg./kg.

Enhancement of local anesthesia. Hotovy (1956) devised a method that depends on an enhancement and prolongation of the local anesthetic effect produced in the cornea of rabbits with Nupercaine. Acetylsalicylic acid and other analgesics give a positive effect when evaluated by this method. Carisoprodol was studied by use of a modification of this technique. Solutions of the drugs were injected into the ear vein of male white rabbits weighing 2 to 3 kg. Carisoprodol was dissolved in propylene glycol. Immediately after injection of the drug, 3 drops of 0.01 per cent Nupercaine were applied to the conjunctival sac of one eye and the eyelids held closed for 30 sec. The sensitivity of the cornea was then tested by light stroking across the middle of the cornea with a very fine glass rod. The cornea was stroked 3 times in succession at 5-min. intervals until a positive response—blinking or closing of the lid—was obtained. The untreated eye was also tested to note any systemic action of the drug.

TABLE 6

EFFECT OF DRUGS ON DURATION OF LOCAL ANESTHESIA PRODUCED BY NUPERCAINE ON THE RABBIT CORNEA

	Number of rabbits	Duration of local anesthesia (min.)
Control	10	14.9 ± 2.8
Morphine, 5 mg./kg.	10	48.0 ± 7.0
Carisoprodol, 37 mg./kg.	5	5.0 ± 2.0
Carisoprodol, 75 mg./kg.	5	3.4 ± 2.0
Propylene glycol, 0.4 ml./kg.	5	11.0 ± 2.0

Unexpectedly, carisoprodol shortened the duration of corneal insensitivity. Morphine, on the other hand, greatly increased the duration of the local anesthesia. These results are summarized in TABLE 6.

Hot plate method. The effect of carisoprodol on the withdrawal reaction produced in mice placed on a hot plate was investigated according to the method of Woolfe and MacDonald (1944). The hot plate was maintained at 53.5 ± 0.5° C. and a mouse was considered to show analgesia if it was able to remain on the hot plate for 30 sec. without showing the characteristic kicking movements of the hind legs. At least 10 mice were used at each dose level. Drugs were given intraperitoneally suspended in 5 per cent gum acacia.

Carisoprodol did not produce analgesia in any of the animals receiving 50 or 100 mg./kg. On the contrary, mice receiving the drug appeared to react to the heat somewhat more rapidly than untreated control animals. This increased reactivity indicates that muscular relaxation at this dose level does not interfere in any way with the responsiveness of the animal to stimulation.

To uncover any latent analgesic activity, the effect of carisoprodol given jointly with codeine was investigated. Codeine is known to produce easily discernible analgesia with this test procedure. By giving the drug to groups of mice at graded dose levels, the 50 per cent effective dose could be calculated according to the method of Miller and Tainter (1944). These doses are given in TABLE 7. It will be noted that carisoprodol in doses of 50 mg./kg. significantly increased the analgesic action of codeine. Meprobamate, on the other hand, did not possess any such effect.

Silver-nitrate method. Carisoprodol proved an effective analgesic when evaluated for its ability to relieve pain produced by injection of silver nitrate into joints of rats. The method used was a modification of the one described by LaBelle and Tislow (1950) for the measurement of the anti-inflammatory action of antiarthritic drugs. Male albino rats* weighing 150 to 250 gm. were injected with 0.2 ml. of a silver-nitrate solution into the ankle joint of the hind leg. This produced a painful edematous inflammation. Eighteen hours after injection of the irritant, flexion of the joint produced a pain reaction that was always accompanied by a squeal. Drugs were given orally, and assessment of pain was made at hourly intervals for 5 hours subsequent to the administration of the drug. Absence of a squeal on abrupt flexion of the joint was taken as absence of pain. Groups of animals were treated at various dose levels, and the median effective doses were calculated. The amounts of each drug producing muscular relaxation and ataxia were evaluated by observing limb placement of animals moving across a wide-mesh wire screen. The results of this study are given in TABLE 8.

TABLE 7

EFFECT OF CODEINE SULFATE GIVEN ALONE OR JOINTLY WITH CARISOPRODOL OR MEPROBAMATE ON THE REACTION OF MICE TO HEAT*

	No. of mice with analgesia/ No. of mice used	Mean analgesic dose ± S.E.
Codeine, 10 mg./kg.	0/30	
Codeine, 16 mg./kg.	12/30	19.0 ± 0.96
Codeine, 24 mg./kg.	20/30	
Carisoprodol, 50 mg./kg.	0/10	—
Meprobamate, 50 mg./kg.	0/10	—
Codeine, 7 mg./kg., + carisoprodol, 50 mg./kg.	1/30	
Codeine, 10 mg./kg., + carisoprodol, 50 mg./kg.	6/30	13.9 ± 0.93
Codeine, 16 mg./kg., + carisoprodol, 50 mg./kg.	19/30	
Codeine, 10 mg./kg., + meprobamate, 50 mg./kg.	4/30	
Codeine, 16 mg./kg., + meprobamate, 50 mg./kg.	12/30	19.3 ± 1.79
Codeine, 24 mg./kg., + meprobamate, 50 mg./kg.	19/30	

* Evaluated according to the procedure of Woolfe and MacDonald (1944).

Carisoprodol effectively relieved pain in doses that did not produce ataxia, muscular relaxation, or paralysis. The pain relief produced by carisoprodol could not be due to relief of the muscle spasm because analgesia was observed clearly after the administration of doses too small to affect muscle tone. Meprobamate and pentobarbital were able to produce analgesia only in doses that also produced neurological deficits and ataxia. Acetylsalicylic acid produced analgesia only when given in high doses close to the toxic level of the drug.

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* Obtained from Dierolf Farms, Boyertown, Pa.

Effect on tooth-pulp threshold in man. Carisoprodol and other analgesics were evaluated for their ability to abolish pain produced by electric stimulation of the tooth pulp (Margolin, 1960). These studies employed a current generator having a resistance of over 3 million ohms incorporated in the circuit.* This high resistance maintained the actual current in the circuit at about 4 microamperes. The variations in resistance of the tooth pulp in relation to this high resistance were slight, so that variations of the current were not appreciable. The right upper central incisor was stimulated at gradually increasing voltages for a period of 2 sec. at intervals of 5 to 10 sec. until the subject reported pain. The subjects were 19 healthy men and women, 22 to 52 years of age, and the double-unknown technique was employed, whereby neither the subjects nor the observer knew whether a drug or placebo was being used. In the first experiment, sugar-coated tablets containing carisoprodol or lactose were given. The placebo and drug tablets were indistinguishable from each other in appearance and shape. In the second experiment, codeine phosphate, acetylsalicylic acid, meprobamate, or lactose were given in capsules of similar appearance. The tests were carried out in the morning after breakfast, and the subjects were not permitted to take any food during the experiments. The pain threshold was measured just before administration of the drug and 1 and 2 hours afterward. At least 6 days were allowed to elapse between the evaluation of each drug or placebo. The subjects were not informed about the data obtained. The readings were expressed in terms of threshold changes from the original scores and their significance was evaluated with the use of standard statistical techniques.

TABLE 8

ANALGESIC ACTION OF DRUGS AGAINST PAIN PRODUCED BY SILVER-NITRATE INJECTION INTO JOINTS OF RATS, AND MEAN DOSES PRODUCING ATAXIA

Compound	ED_{50} for analgesia (mg./kg.)	ED_{50} for ataxia (mg./kg.)
Acetylsalicylic acid	415 ± 38	—
Carisoprodol	130 ± 15	520 ± 51
Meprobamate	150 ± 18	140 ± 11
Pentobarbital	29 ± 7	29 ± 7

The results are illustrated in TABLE 9 and FIGURE 6. Carisoprodol, 700 mg., elevated the threshold to painful stimulation of the tooth pulp significantly at 1 and 2 hours after administration of the drug. Codeine phosphate, 30 mg., had a similar effect, but appeared somewhat more effective in elevating the threshold after 1 hour and less effective than carisoprodol 2 hours after administration. Acetylsalicylic acid, 600 mg., produced a small increase in threshold that was not statistically significant. Meprobamate, 800 mg., did not increase the pain threshold.

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* This generator is commercially available under the name of Vitalometer from Burton Mfg. Co., Santa Monica, Calif.

In these experiments an end point was utilized that does not depend on any muscular reaction. Thus it appears that carisoprodol can exert its analgesic properties in humans independently of its muscle relaxant action.

Selective effects on electroencephalogram activation. Silvestrini and Longo (1956) have shown that morphine selectively blocks the arousal reaction produced by painful stimuli while leaving intact the arousal produced by other stimuli such as touch or sound. It was of interest to see whether carisoprodol and other central nervous depressants such as barbiturates showed a similar selectivity.

Sixteen adult male rabbits were used in this study. Needle electrodes were nserted through burr holes and the sciatic nerve was prepared for stimulation under local anesthesia. The animals were not curarized and were permitted to rest quietly in a darkened room. Bipolar recordings were taken on a Grass Model 3D electroencephalograph. Sciatic stimuli were single-shock square waves of 0.5 msec. duration. Other noxious stimuli were ear pinching, by means of a hemostat with jaws protected by rubber tubing, and a thermal stimulus of a water-filled test tube at about 70° C. applied to the ear. The nonpainful stimuli were a brief puff of air from a pressurized can of Freon held about 4 inches from the rabbit's face, an acoustic stimulus produced by the ring of a toy pistol, and the stroking of the rabbit's back for about 5 sec. All rugs were given intravenously. Carisoprodol and meprobamate were dissolved in 50 per cent propylene glycol.

TABLE 9

ELEVATION BY DRUGS OF THRESHOLD IN HUMANS FOR PAIN PRODUCED BY ELECTRIC STIMULATION OF TOOTH PULP

Preparation	Dose	Pain threshold			
		After 60 min. (%)	t	After 120 min. (%)	t
Carisoprodol	700 mg. (tablets)	113 ± 9.4*	2.15	151 ± 20.5*	2.33
Placebo (lactose)	2 tablets	87 ± 7.8†	—	99 ± 8.8	—
Placebo (lactose)	2 capsules	99 ± 5.8	—	103 ± 7.2	—
Codeine phosphate	30 mg. (capsules)	128 ± 8.3*	2.48	130 ± 10.1*	2.21
Acetylsalicylic acid	600 mg. (capsules)	108 ± 7.2	0.98	109 ± 9.2	0.51
Meprobamate	800 mg. (capsules)	87 ± 6.1	1.38	100 ± 7.4	0.29

* Differs significantly from appropriate placebo: $p \leqq 0.05$.
† Not significantly different from capsule placebo: $t = 1.23$, $p > 0.2$.

The resting rabbits' high-voltage, slow brain-wave pattern is changed by a sensory stimulus of adequate intensity to a high-frequency, low-voltage pattern that usually outlasts the duration of the stimulus by several seconds. The activation response elicited by stimulation of the sciatic nerve at threshld voltages could be suppressed completely or nearly completely by all drugs except meprobamate. When the intensity of stimulation was increased, some activation was usually obtained. The degree of depression of the activation response evoked by innocuous stimuli depended upon the drug administered. There was some variation from animal to animal in the effectiveness of the ifferent stimuli in producing activation. In some, for example, stroking was a poor stimulus, and an air puff a good one; in others this was reversed. Sciatic stimulation was the most consistent in eliciting activation at intensities that varied but little from rabbit to rabbit.

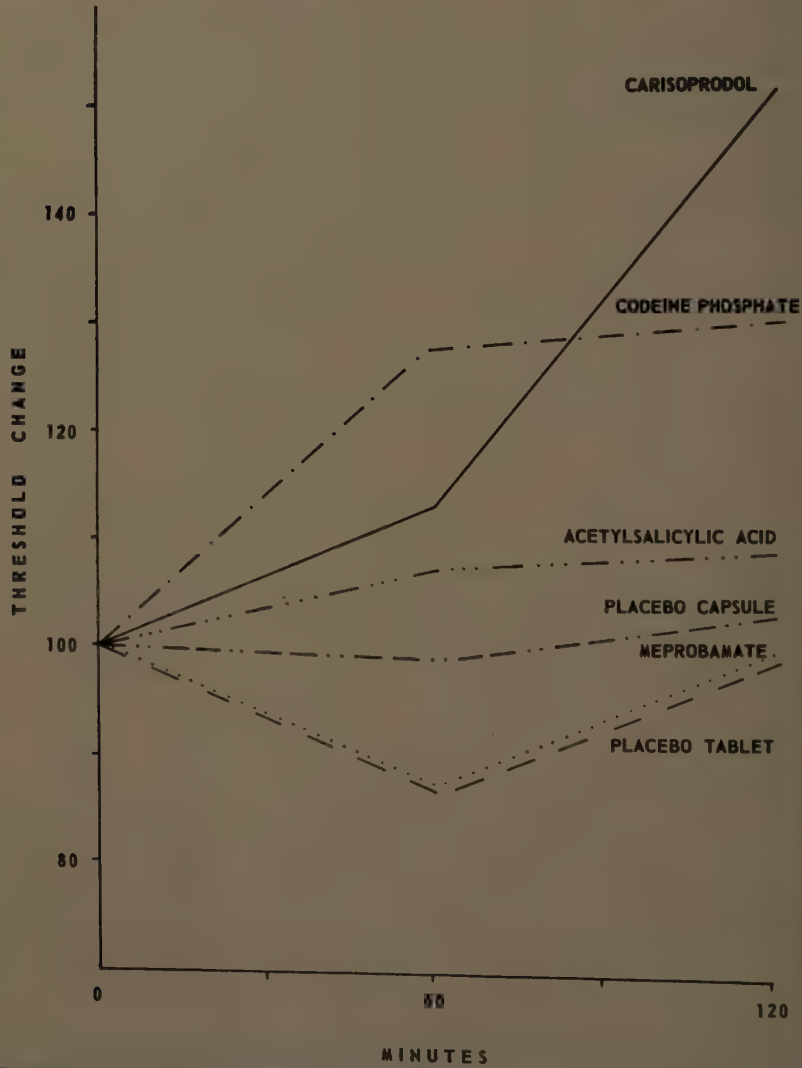

FIGURE 6. Elevation of threshold to painful electric stimulation of the tooth pulp by drugs in human beings. Doses: carisoprodol, 700 mg.; codeine phosphate, 30 mg.; acetylsalicylic acid, 600 mg.; meprobamate, 800 mg.

The stimulating voltage required for single-shock activation via the sciatic nerve prior to the administration of drugs was usually about 0.5 v. After 5 mg./kg. of morphine, a stimulus strength of 3 or 4 v. usually was required to produce signs of activation. Carisoprodol, 10 mg./kg., raised the threshold for sciatic activation to 2 to 3 v. Pentobarbital in doses of 6 mg./kg. raised the required activation to 1 or 2 v. With these doses of the drugs, good activation responses were still obtained with the nonpainful stimuli given at intensities similar to those prior to the administration of drugs. When the doses of these drugs were sufficiently increased, however, all selectivity vanished, and only generalized depression was seen.

It was then possible to find a dose of morphine, carisoprodol, or pentobarbital that preferentially depressed activation of the electroencephalogram when pain was used as the stimulus, but affected activation only slightly or not at all when nonpainful stimuli, such as an air puff or stroking, were applied. There were, however, marked quantitative differences between the drugs, as indicated by the increase in voltage required to produce activation through stimulation of the sciatic nerve after administration of the drugs. On this basis morphine showed greatest selectivity, carisoprodol somewhat less selectivity, and pentobarbital some selectivity. Meprobamate, 10 mg./kg., had no effect on activation. Atropine, 0.5 mg./kg., showed no selectivity and depressed painful and nonpainful responses equally. In higher doses of 1 mg./kg. it abolished the activation response entirely.

TABLE 10

COMPARISON OF VARIOUS PROPERTIES OF ANTIPYRETIC ANALGESICS AND NARCOTIC ANALGESICS WITH CARISOPRODOL*

	Antipyretic analgesics	Narcotic analgesics	Carisoprodol
Antipyretic action	+	−	−
Writhing suppression	+	+	−
Local anesthesia prolongation	+	+	−
Withdrawal reflexes suppression	−	+	−
Codeine synergism	−	+	+
Joint pain test†	+	+	+
Selectivity on EEG activation	−	+	+
Muscle relaxation	−	−	+
Anti-inflammatory action	+	−	−
Uricosuric action	+	−	−
Autonomic effects	−	+	−

* Key: + means present, effective, or raised; − means absent, ineffective, or unchanged.

† Pain produced by injection of silver nitrate (see text).

In summary, carisoprodol, in doses of 10 mg./kg., depressed the activation response to sciatic stimulation more than the response to nonpainful stimuli. Morphine in doses of 5 mg./kg. exhibited the same effect, but showed a wider margin between the threshold for sciatic activation and the retention of nonpainful responses. Pentobarbital in doses of 3 to 6 mg./kg. showed only slight selectivity. With all drugs selectivity could be shown only with carefully graded doses.

Anti-inflammatory action. Carisoprodol did not appear to have marked anti-inflammatory action. It did not alter the dermal spreading action of hyaluronidase carried out as described by Asboe-Hansen (1952) and did not inhibit granuloma tissue formation in rabbits when evaluated according to the method of Meyer *et al.* (1953). Unlike salicylates, it did not significantly decrease either the level of circulating eosinophils or the adrenal ascorbic acid level in rats. It was also without effect on the migration of human leukocytes and had no influence on the Schwartzman phenomenon.

Comparison with other analgesics. The analgesic properties of carisoprodol are different from those of the antipyretics or opium alkaloids, and these differences make it necessary to classify the drug apart from the agents used thus far. Carisoprodol differs from the antipyretic analgesics in possessing no anti-inflammatory action, in having only an unimportant antipyretic action, and in producing its analgesic effect by an action on the central nervous system. Carisoprodol differs from the narcotic analgesics in not affecting the withdrawal reflexes and in having little effect on the peripheral autonomic nervous system. These properties are summarized in TABLE 10.

In chemical structure the carisoprodol molecule differs from that of the accepted analgesics in not possessing a ring structure.

Conclusion and Summary

Until recently it was customary to discard drugs that were devoid of antipyretic action and that did not abolish the natural defense reflexes to painful stimuli as agents devoid of analgesic properties. Carisoprodol, although devoid of these two properties, has been shown to possess clear-cut analgesic action in suitably designed assay procedures in animals. The analgesic action of the drug has also been confirmed in humans. In addition, carisoprodol possesses muscle relaxant properties that are qualitatively different from those of other accepted centrally acting skeletal muscle relaxants. The analgesic properties of carisoprodol are, however, independent of its muscle relaxant action. Neuropharmacological analysis of the effects of carisoprodol on the central nervous system indicates that the drug produces effects that are quite different from those observed after administration of meprobamate, to which it is related chemically.

References

ASBOE-HANSEN, G. 1952. Influence of ACTH and cortisone on dermal spread: suppressed action of hyaluronidase due to connective tissue changes. Acta Endocrinol. **9:** 29–36.

BERGER, F. M. 1947. The mode of action of Myanesin. Brit. J. Pharmacol. **2:** 241–250.

BERGER, F. M. 1949. Anticonvulsant action of 2-substituted-1,3-propanediols. Proc. Soc. Exptl. Biol. Med. **71:** 270–271.

BERGER, F. M. 1949. Spinal cord depressant drugs. J. Pharmacol. Exptl. Therap. **96:** 243–278.

BERGER, F. M. 1952. Central depressant properties of *o*-toloxypropyl carbamates. J. Pharmacol. Exptl. Therap. **104:** 468–473.

BERGER, F. M. 1954. The pharmacological properties of 2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate (Miltown), a new interneuronal blocking agent. J. Pharmacol. Exptl. Therap. **112:** 413–423.

BERGER, F. M. 1956. Meprobamate, its pharmacological properties and clinical uses. Intern. Record Med. **169:** 184–196.

BERGER, F. M. 1959. The muscle relaxant and analgesic properties of carisoprodol. J. G. Miller, Ed. *In* The Pharmacology and Clinical Usefulness of Carisoprodol. : 25–37. Wayne State Univ. Press. Detroit, Mich

BERGER, F. M. & W. BRADLEY. 1946. The pharmacological properties of $\alpha:\beta$ dihydroxy-α-(2-methylphenoxy)-propane (Myanesin). Brit. J. Pharmacol. **1:** 265–272.

BERGER, F. M., M. KLETZKIN, B. J. LUDWIG, S. MARGOLIN & L. S. POWELL. 1959. Some unusual pharmacological properties of N-isopropyl-2-methyl-2-propyl-1,3 propanediol dicarbamate (Soma). J. Pharmacol. Exptl. Therap. **127:** 66–73.

BRADLEY, P. B. & J. ELKES. 1957. The effects of some drugs on the electrical activity of the brain. Brain. **80:** 77–117.

Brownlee, G. 1937. Comparison of antipyretic activity and toxicity of phenacetin and aspirin. Quart. J. Pharm. Pharmacol. **10:** 609–620.

Brownlee, G. 1939. Therapeutic index for coal tar antipyretics. Quart. J. Pharm. Pharmacol. **12:** 45–60.

del Castillo Nicolau, J. 1948. Acciones centrales de la mianesina. Arch. med. exptl. (Madrid). **11:** 363–385.

Gangloff, H. 1958. Effect of meprobamate and phenaglycodol on spontaneous and evoked brain activity in the cat. Federation Proc. **17:** 369.

Gangloff, H. 1959. Effect of phenaglycodol and meprobamate on spontaneous brain activity, evoked EEG arousal and recruitment in the cat. J. Pharmacol. Exptl. Therap. **126:** 30–40.

Hendley, C. D., T. E. Lynes & F. M. Berger. 1954. Effect of 2 methyl-2-*n*-propyl-1,3-propanediol dicarbamate (Miltown) on central nervous system. Proc. Soc. Exptl. Biol. Med. **87:** 608–610.

Hendley, C. D., T. E. Lynes & F. M. Berger. 1957. Effect of meprobamate on electrical activity of the thalamus and other subcortical areas. : 35–46. H. E. Himwich, Ed. *In* Tranquilizing Drugs. Am. Assoc. Advancement of Sci.

Hotovy, R. 1956. Messung zentralanalgetischer Wirkungen mit der Regnierschen Methode. Arch. exptl. Pathol. Pharmakol. Naunyn-Schmiedeberg's. **228:** 387–402.

Kletzkin, M. & F. M. Berger. 1959. Effect of meprobamate on the limbic system of the brain. Proc. Soc. Exptl. Biol. Med. **100:** 681–683.

LaBelle, A. & R. Tislow. 1950. A method of evaluating analgesics of the antiarthralgic type in the laboratory animal. J. Pharmacol. Exptl. Therap. **98:** 19–21.

Longo, V. G. 1956. Effects of scopolamine and atropine on electroencephalographic and behavioral reactions due to hypothalamic stimulation. J. Pharmacol. Exptl. Therap. **116:** 198–208.

Makovsky, A. & S. Margolin. 1954. Quantitative determination of oral antisalagogue activity in non-anesthetized mice. Federation Proc. **13:** 382.

Margolin, S. 1960. Effect of carisoprodol and other analgesics upon tooth pulp pain in humans. Federation Proc. **19:**. In press.

Marsh, D. V. 1955. Comparative pharmacological activity of 2-amino-5-chlorobenzoxazole (McN 485) and other mephenesin-like agents. Federation Proc. **14:** 366.

Meyer, R. K., J. C. Stucki & K. Aulsebrook. 1953. Effect of pregnancy and lactation on granuloma tissue formation and joint permeability in rats. Proc. Soc. Exptl. Biol. Med. **84:** 624–628.

Miller, L. C. & M. C. Tainter. 1944. Estimation of the ED_{50} and its error by means of logarithmic probit graph paper. Proc. Soc. Exptl. Biol. Med. **57:** 261–264.

Siegmund, E., R. Cadmus & G. Lu. 1957. A method for evaluating both narcotic and non-narcotic analgesics. Proc. Soc. Exptl. Biol. Med. **95:** 729–731.

Silvestrini, B. & V. G. Longo. 1956. Selective activity of morphine on EEG arousal reaction to painful stimuli. Experientia. **12:** 436–438.

Wescoe, W. C., R. E. Green, B. P. McNamara & S. Krop. 1948. Influence of atropine and scopolamine on central effects of DFP. J. Pharmacol. Exptl. Therap. **92:** 63–72.

Woolfe, G. & A. D. Macdonald. 1944. Evaluation of analgesic action of pethidine hydrochloride (Demerol). J. Pharmacol. Exptl. Therap. **80:** 300–307.

THE MODE OF ACTION OF CARISOPRODOL*

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Strictly speaking, the mechanism of action of a drug is understood only when we are able to explain its gross pharmacological effects on organic functions in terms of changes elicited at a cellular or subcellular level or, at least, at whatever level the current physiological analysis of those functions happens to be operating. In this sense the title of this contribution is far from being justified. We must admit that we cannot offer an explanation of the mode of action of carisoprodol in terms of present-day knowledge of the physiology of the nerve cells and synaptic junctions. Before we attempt to do that, we must discover on which cellular aggregates within the central nervous system the action of carisoprodol is more pronounced, and what is the general nature of the changes elicited by that compound on those neuronal systems. Only by doing so shall we know what types of experiments are likely to yield more information and what we should look for in those experiments. This paper describes the first exploratory steps in this direction.

The most remarkable single action of carisoprodol in the laboratory is its powerful lytic action on decerebrate rigidity (Berger *et al.*, 1959). The spasm of the extensor muscles of decerebrate cats is abolished by the administration of as little as 3 mg./kg. of carisoprodol; that is, about one-eighth of the amount of mephenesin or meprobamate required to obtain a similar effect. The major aim of this work was to investigate the nature of this action. We have tested, separately, the actions of carisoprodol upon some of the neural mechanisms known to play a role in the production of decerebrate rigidity, attempting to find significant differences in their sensitivity to that compound.

METHODS

Although many details are not yet fully understood, there seems to be no serious disagreement as to the basic arrangement and general functions of the central nervous mechanisms involved in the maintenance and control of muscle tonus or as to why the transection of the brain stem results in decerebrate rigidity. The current knowledge on this problem indicates that a preliminary investigation of the mode of action of a drug acting upon decerebrate rigidity must include a test of its effects upon spinal and brain stem mechanisms.

Adult cats, 2 to 4 kg., either decerebrate or lightly anesthetized with Nembutal, have been used throughout these experiments. Decerebrate animals were usually prepared by intercollicular section of the brain stem under light ether anesthesia. In some experiments a short-acting barbiturate, Sodium Pentothal, in doses of up to 30 mg./kg. was used in place of ether. Nembutal was given in single doses of 20 to 25 mg./kg., being reinforced during preliminary surgery with small doses of Sodium Pentothal. The animals were then mounted in a frame on which the myographs for recording spinal reflexes were

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fixed at one end and the stereotaxic device for the implantation of electrodes in the brain stem was secured to the opposite end.

Spinal Reflexes

To study the action of carisoprodol upon the reflex excitability of the spinal cord, the flexor, crossed extensor, and patellar reflexes were elicited at regular intervals before and after carisoprodol was given to the preparation by intravenous injection. The technique used to record these reflexes was similar to that described by one of us (del Castillo, 1948); one of the hind legs of the preparation was attached, at the lower end of the tibia, to a torsion (semi-isometric) myograph writing on a smoked drum. This leg was used to record, alternately, the knee jerk and crossed extensor reflex. The knee jerk was elicited by tapping the patellar tendon with an electrically operated hammer. The crossed extensor reflex was evoked by the electric stimulation of the central end of the contralateral sciatic nerve. This same stimulus was used to produce an ipsilateral flexor reflex that was recorded by attaching the tendon of the tibialis anticus muscle to another myograph.

Stimulation of the Brain Stem

In other experiments we recorded the effects of the electric stimulation of the brain stem upon the patellar reflex, and studied the influence of carisoprodol on these influences. For this purpose, two monopolar stimulating electrodes made of insulated platinum or Nichrome alloy, gauge No. 24 wire, were used. One of them was placed in the spinal inhibitory area of the medulla after the floor of the fourth ventricle had been exposed through the foramen magnum. The electrode was positioned by visual control, and the final location of its tip was determined by trial and error, watching the effects of stimulation. A second electrode, for the stimulation of spinal facilitative areas of the tegmentum of the pons and midbrain, was placed with the help of a stereotaxic device. The extent and limits, in terms of stereotaxic coordinates, of the spinal facilitative areas of the brain stem are well known and require no discussion here. These coordinates were used as a rough guide for the approximate positioning of the electrode and optimal facilitative sites were then found by trial and error. The stimuli delivered to the electrodes consisted of negative rectangular pulses generated by a set of Textronix 160's units. The duration of the applied pulses was usually kept under 1 msec., their frequency did not exceed 100 cps, and the imposed voltage varied between 2 and 8 v. These 3 parameters were varied separately until the best combination was obtained. In some experiments a weak positive bias current was used in order to counteract possible electrolytic effects caused by unidirectional stimulating pulses. However, no obvious benefits were noticed, and the practice was discontinued. Stimulating electrodes have often been kept in the same site in the brain stem for periods of up to 4 hours without appreciable change in the efficiency of the stimulation.

The procedure usually followed in these experiments was to elicit the patellar reflex at intervals of about 4 sec. The inhibitory or facilitative stimulation was switched on for periods equal to 1 or 2 intervals between successive patellar reflexes (that is, 4 or 8 sec.), allowing a longer period between consecutive stimulations. The switches controlling the stimulation were operated manually in some experiments. However, more recently, we have used a mechanical switching device that could be set to trigger any desired sequence of events. In some experiments only facilitative or inhibitory stimulation was applied. In others, however, 2 electrodes were used to deliver, alternately, facilitative and inhibitory stimulation.

Once the electrode tips were placed in the desired sites of the brain stem, the effects of stimulation were followed for a number of cycles to be certain they were consistent and stable. Very often, marked effects could be obtained just after a site had been located, but the efficiency of the stimuli was soon lost. This probably was due to local mechanical damage. If the effects of stimulation were constant over a number of cycles, the drug was injected without interrupting the stimulation sequence.

Results

A. Effects of Carisoprodol on Spinal Reflexes

The actions of carisoprodol upon flexor, crossed extensor, and patellar reflexes were studied on both decerebrate and Nembutalized preparations.

Decerebrate preparations. Carisoprodol was given to decerebrate preparations at the same doses or at doses slightly higher than are required to abolish rigidity (3 to 5 mg./kg.). The results obtained with these amounts are somewhat variable and, on the whole, not very impressive. FIGURE 1, for instance, illustrates the results of injecting 5 mg./kg. of carisoprodol into a preparation which had a fair degree of rigidity and reflex activity. A slight reduction in muscle tonus occurs just after the injection, accompanied by a decrement of 15 to 20 per cent in the amplitude of the patellar reflex. The flexor and crossed extensor reflexes are not affected appreciably by the drug. FIGURE 1 reveals also a feature of the action of carisoprodol that proved to be constant throughout all our experiments: the effects of the injection of this compound are very rapid, reaching a maximum within 2 or 3 min. In contrast with FIGURE 1, in the experiment illustrated in FIGURE 2, carisoprodol is seen to elicit a decrease of more than 50 per cent in the amplitude of the crossed extensor reflex and a slight depression of the flexor reflex. Recovery took place in about 40 min.

Preparations anesthetized with Nembutal. In cats anesthetized with Nembutal (25 mg./kg.) the injection of small doses of carisoprodol does not result in any appreciable effects on the spinal reflexes.

In the course of the experiments described in *Section B*, which deals with the action of carisoprodol on the effects of brain stem stimulation, we had occasion to study the action of large doses (up to 70 mg./kg.) of carisoprodol upon the patellar reflex of Nembutalized animals. The effects observed with these dosages were extremely variable. In some preparations a reduction in the amplitude of the reflex was observed, whereas in others a definite enhancement was produced.

Interaction between carisoprodol and strychnine. Although carisoprodol is a poor antagonist of strychnine convulsions (Berger *et al.*, 1959) the interaction of these 2 compounds at the spinal level was studied. The effects of carisoprodol upon spinal polysynaptic reflexes selectively potentiated by strychnine proved to be of similar character, but weaker than those that have been demonstrated with mephenesin. FIGURE 3 illustrates an experiment in which the antagonistic action of carisoprodol upon strychnine-potentiated reflexes was

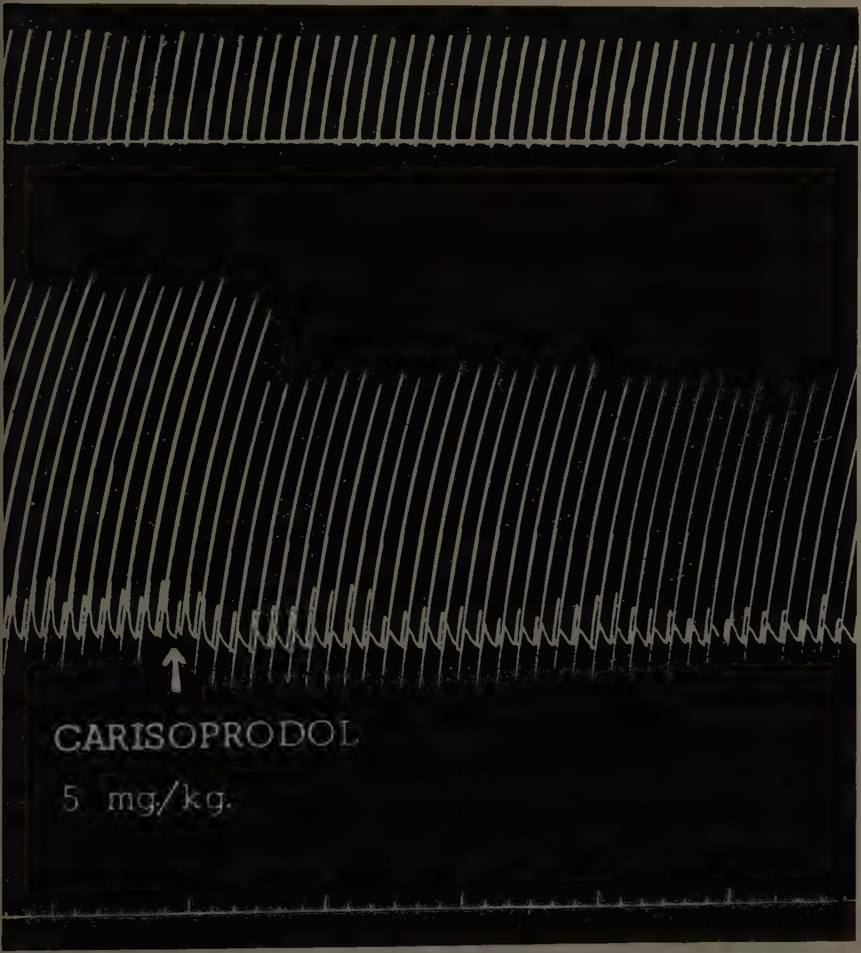

FIGURE 1. Influence of carisoprodol upon spinal reflexes in a decerebrate preparation. *From top to bottom:* flexor, patellar, and crossed extensor reflexes. Time signal: 10 sec. and 1 min. After intravenous injection of 5 mg./kg. of carisoprodol, indicated by the arrow, the muscle tonus is seen to fall slightly. This decrement of muscle tonus is accompanied by a decrease in the amplitude of the knee jerk (*largest vertical lines*). The crossed extensor reflex that can be seen between consecutive knee jerks is not appreciably affected by the drug.

stronger than average. It was performed in a decerebrate preparation in which the crossed extensor reflexes were hardly noticeable. The injection of 0.2 mg./kg. of strychnine resulted in a marked potentiation of those responses and an increase in muscle tonus. The injection of 5 mg./kg. of carisoprodol reversed temporarily the effects of strychnine. On other occasions, only slight

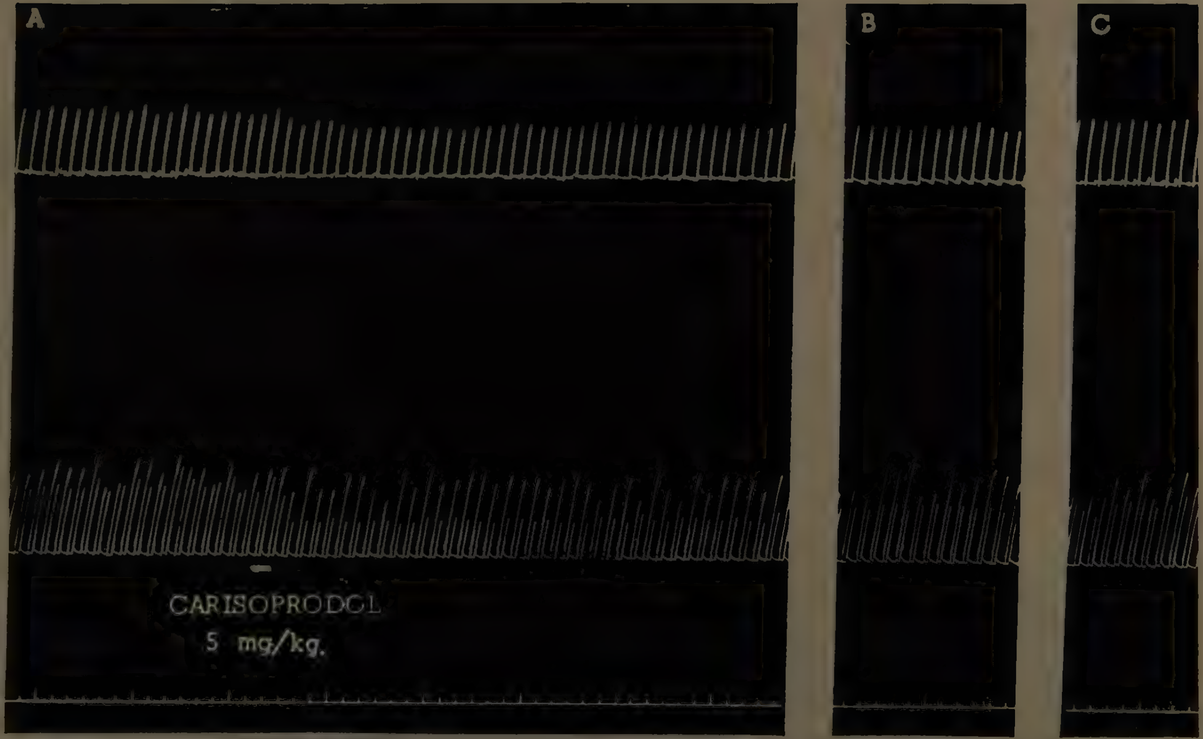

Figure 2. Influence of carisoprodol upon the spinal reflexes in a decerebrate preparation (cat, 3 kg.). *From top to bottom:* flexor reflex, knee jerk, and crossed extensor reflex. Time signal: 10 sec. and 1 min. Carisoprodol (5 mg./kg.) was injected in A as shown. The knee jerk is not appreciably affected by the drug. The crossed extensor reflex is reduced by about 50 per cent. A slight reduction in the height of the flexor reflex is also observed. Records B and C were taken 15 and 50 min., respectively, after the injection of carisoprodol.

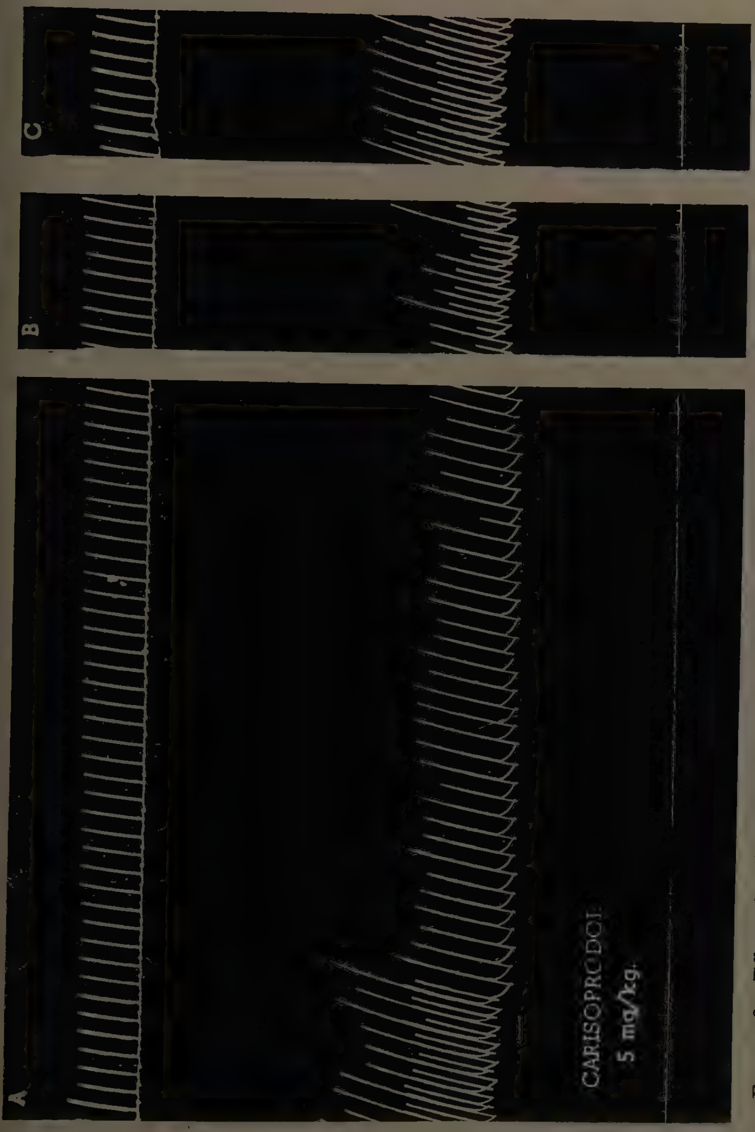

FIGURE 3. Effect of carisoprodol upon the strychnine-potentiated crossed extensor reflex. *From top to bottom:* flexor, patellar, and crossed extensor reflexes. Time signal: 10 sec. and 1 min. Records B and C were taken 25 and 45 min., respectively, after injection of carisoprodol.

reductions in the amplitude of this reflex, similar to those observed in untreated preparations, could be observed.

Action of carisoprodol upon the spinal reflexes potentiated by eserine. As Schweitzer and Wright (1937) demonstrated and Wilker (1945) confirmed, the injection of eserine at doses of up to 0.25 mg./kg. results in a marked increase in the reflex excitability of the spinal cord, and particularly in a large enhancement of monosynaptic reflexes. Higher doses may result in an increase of muscle tonus and convulsive movements.

The existence of an antagonism between mephenesin and eserine was demonstrated in the intact animal by Berger and Bradley (1946) and in the spinal reflexes of decerebrate preparations by one of us (del Castillo, 1948). It was interesting, therefore, to see whether carisoprodol would also possess a similar antagonistic action. With this purpose, eserine was injected at doses varying between 0.1 and 0.2 mg./kg. into decerebrate preparations. Almost invariably the injection of the anticholinesterase was followed by a very marked potentiation of spinal reflex responses, particularly the knee jerk. Carisoprodol was found to antagonize this effect completely in doses varying between 5 and 10 mg./kg. This is shown in FIGURE 4 where it can be seen how the amplitude of the potentiated reflexes falls below the original level after the second of two 5-mg./kg. injections of carisoprodol. The efficacy of carisoprodol in counteracting the spinal actions of anticholinesterases seems to be greater than that shown by mephenesin (*cf.* Figure 9 of del Castillo, 1948, where 100 mg./kg. of mephenesin fails to antagonize completely the effect of 0.2 mg./kg. of eserine).

Although carisoprodol behaves peripherally as a very weak cholinergic blocking agent (Berger *et al.*, 1959), it has definite atropinelike effects upon the central nervous system, blocking ascending (that is, activating) reticular pathways. For instance, the injection of carisoprodol is followed, not accompanied by, behavioral effects, according to high-voltage and low-frequency EEG patterns. We wondered, therefore, whether the antagonistic effect of carisoprodol upon the eserine-potentiated spinal reflexes might not represent another aspect of its anticholinergic effects on the central nervous system. In some experiments, atropine in doses of up to 1 mg./kg. was injected into decerebrate preparations, either before the administration of eserine or after the reflexes had been potentiated by the anticholinesterase. In agreement with the observations of Schweitzer and Wright (1937), atropine did not prevent the potentiation of monosynaptic reflexes by the injection of eserine, and it has only a very weak and inconsistent antagonistic action if it is given after the reflex responses have been potentiated. In some of these experiments, after atropine was found to be inactive, carisoprodol was injected. It was surprising to see that under these conditions carisoprodol failed to counteract the potentiation of reflexes induced by eserine. In some instances, the injection of as much as 20 mg./kg. of carisoprodol did not show any clear effect on the potentiated responses. In others, only delayed and doubtful effects were observed. Although we have not yet investigated these observations in detail, they are cited here because of their potential clinical interest.

From the experiments just described it may be concluded that carisoprodol exerts a slight but definite effect upon the reflex excitability of the spinal cord, an effect that qualitatively resembles that elicited by other muscle-relaxant agents. It seems unlikely, however, that the dramatic action of low doses of that compound upon decerebrate rigidity could be explained entirely on the basis of spinal actions. Therefore, the next stage of this investigation was devoted to studying the actions of carisoprodol upon the modifications produced in spinal reflexes by the electric stimulation of the facilitative and inhibitory areas of the brain stem.

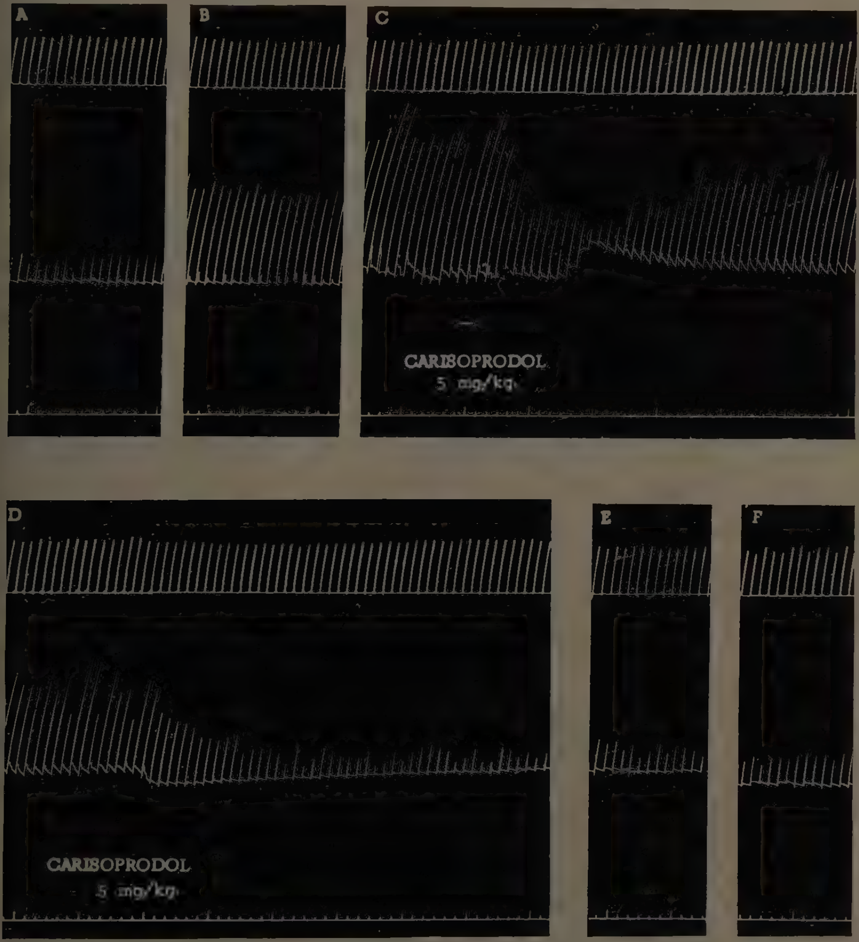

Figure 4. Antagonism between carisoprodol and eserine (decerebrated cat). *Upper record:* flexor reflex. *Lower record:* patellar reflex. At some points a small crossed extensor reflex elicited by the same stimulus that evokes the ipsilateral flexor reflex is observed (*see text*). Record A shows the amplitude of the reflexes at the beginning of the experiment. The preparation was showing a low degree of spinal excitability. Between A and B and between B and C two doses of eserine, 0.15 and 0.10 mg./kg., respectively, were injected. Note marked potentiation of the patellar reflex following these injections, while the flexor reflex remains unchanged. In C, carisoprodol (5 mg./kg.) is injected. This results in a reduction in the amplitude of the potentiated reflex. In record D beginning 9 min. after the injection, a second and equal dose of carisoprodol was given. The patellar reflex is now reduced to a level even lower than that seen in A. Records E and F were taken 15 and 55 min., respectively, after the second injection of carisoprodol. Time signal: 10 sec. and 1 min.

B. Influence of Carisoprodol upon Spinal Facilitation and Inhibition due to Brain Stem Stimulation

Stimulating electrodes were placed, as indicated under METHODS, on spinal facilitative and inhibitory sites of the brain stem. By careful location of the electrode tips and control of the depth of anesthesia, spinal facilitative and inhibitory patterns closely resembling those described in the original papers of Magoun and his collaborators were obtained (Magoun and Rhines, 1946, 1947; Sprague *et al.*, 1948). Particular attention was given to the influences of the brain stem upon monosynaptic reflexes, and only the patellar reflex was recorded in most of these experiments.

It soon became evident that carisoprodol exerts a marked depressing action upon reticulospinal facilitative influences. In fact, the effects of the stimulation of facilitative areas of the brain stem can be depressed markedly by 10 mg./kg. of carisoprodol and completely blocked by 15 to 20 mg./kg. (see FIGURES 5 and 6).

In some facilitative sites of the brain stem, electric stimulation elicits only large and sustained increments in the extensor tonus of the hind limb without a simultaneous increase in the amplitude of the knee jerk (see *Section D*). The effect of carisoprodol on such changes in tonus is shown in FIGURE 7. Record A shows how repeated stimulation of such a facilitative site results in a gradual decrease in the magnitude of the elicited responses, although a steady level is reached after a few periods. The injection of 20 mg./kg. of carisoprodol abolished the tonic response. Record B, taken 30 min. after the injection of carisoprodol, shows the beginning of recovery; the responses elicited were very small, and the efficiency of the stimuli was quickly lost. Recovery was not complete 120 min. after the injection, as seen in record E; although the first response of a series is rather large, the amplitude of successive responses decays very quickly.

These results resemble closely those obtained by other investigators working with several centrally acting muscle-relaxant agents such as mephenesin (Henneman *et al.*, 1949; Kaada, 1950), 6-methyl-2-aminobenzothiazole (Funderburk *et al.*, 1953; King and Unna, 1954), and 2,2-diethyl-1,3-propanediol (Prenderol), Funderburk and Unna, 1953.

All of these drugs have proved to have a clear suppressing influence upon spinal facilitation. In these experiments, however, the compounds tested showed also, without exception, a depressing effect upon the inhibition of spinal reflexes elicited by the electric stimulation of the medial areas of the medulla.

Therefore, it was interesting to find in our experiments that the inhibition of the patellar reflex induced by stimulation of the medulla is particularly resistant to the action of carisoprodol. Inhibition was not affected even by dosages of this compound as high as 70 mg./kg. In order to learn whether these results might depend upon the particular sensitivities of individual preparations, experiments were performed in which the facilitative and inhibitory areas of the brain stem were stimulated, alternatively, in the same animal. FIGURE 8 illustrates one of these experiments. It shows that although facilitation is suppressed by 20 mg./kg. of carisoprodol, inhibition is not affected even after the injection of a second and equal dose of the drug.

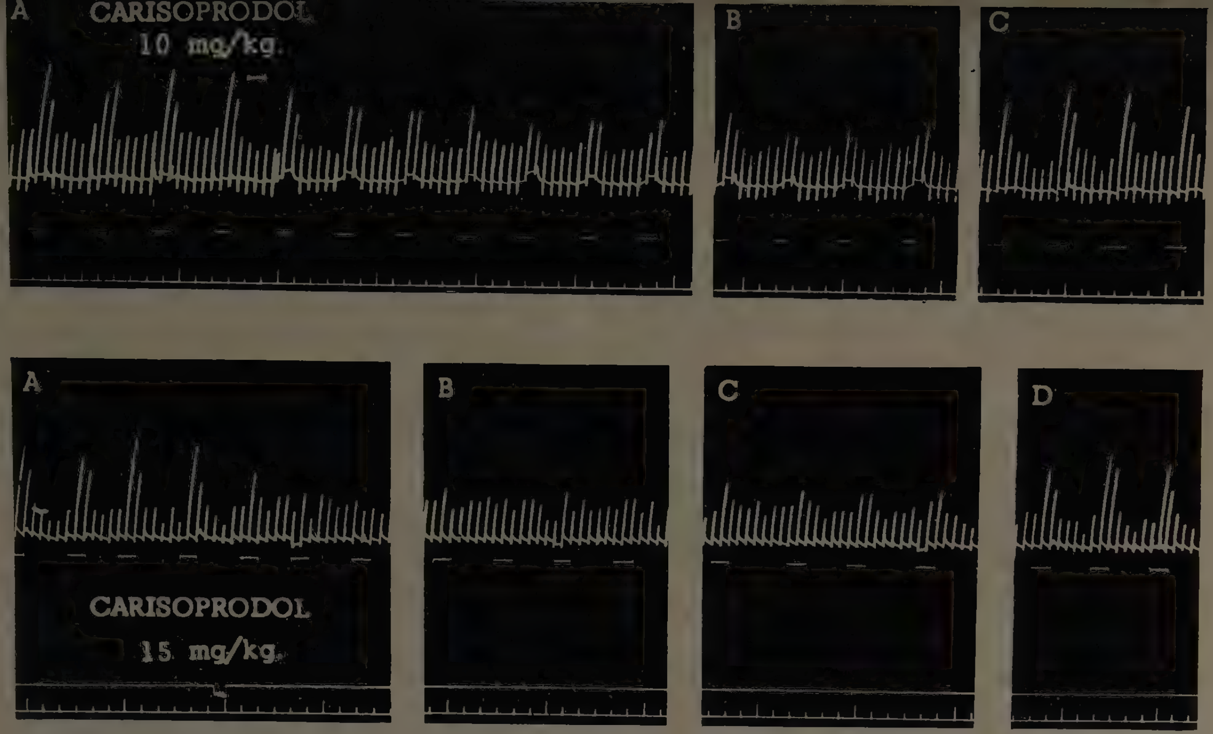

FIGURE 5. Depressant influence of carisoprodol upon reticulospinal facilitation in a Nembutalized preparation. The results of 2 experiments in a cat anesthetized with Nembutal (25 mg./kg.) are illustrated in this figure. The amplitude of the patellar reflex registered continuously during both experiments is seen to increase during the stimulation of facilitative sites in the brain stem, as indicated by horizontal bars. In the experiment shown at the top, the injection of 10 mg./kg. of carisoprodol is seen to produce a marked depression in the degree of facilitation. Records B and C were taken 20 and 60 min., respectively, after the injection. In the experiment illustrated below, the injection of 15 mg./kg. of the drug produced a block of reticulospinal facilitation. Records B, C, and D were taken 15, 40, and 80 min. after the injection. Time signals in both experiments: 10 sec. and 1 min.

Although the doses of carisoprodol required to block reticulospinal facilitation (15 to 20 mg./kg.) were 5 or 6 times larger than those required to abolish decerebrate rigidity, the results of these experiments were considered adequate to explain the effects of carisoprodol upon such a condition. The difference be-

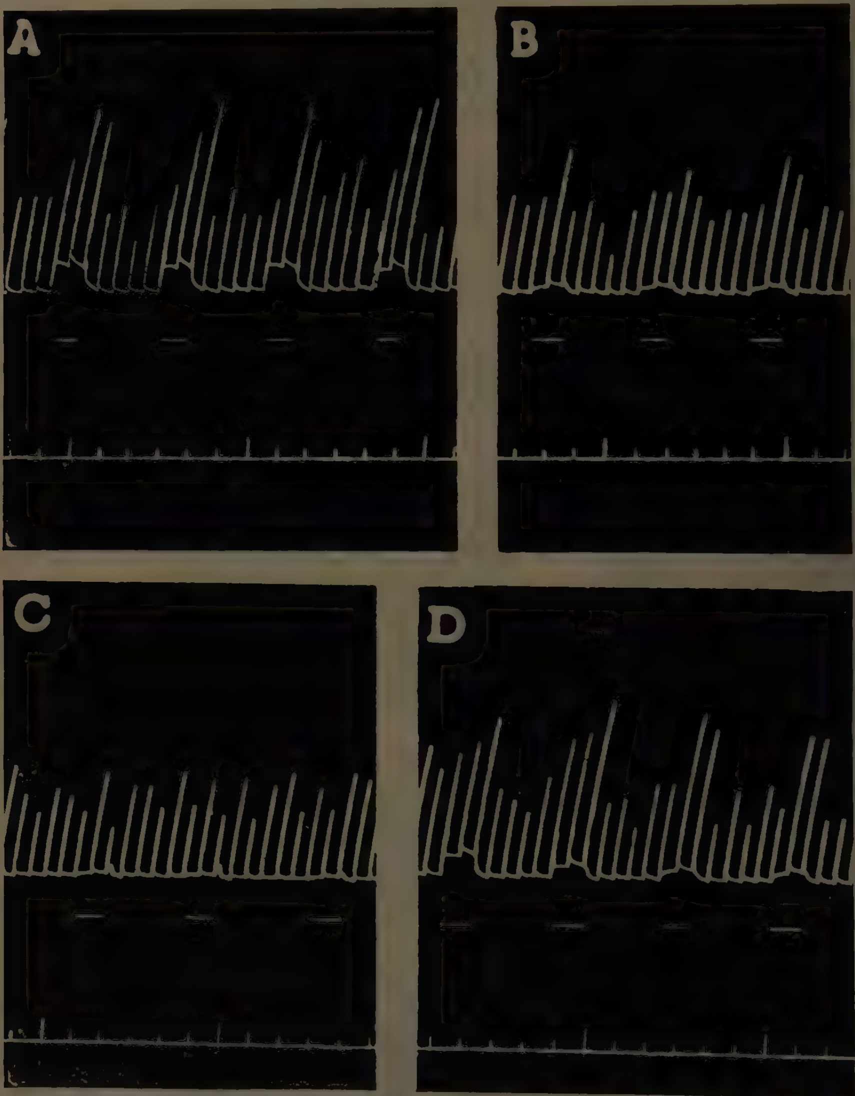

FIGURE 6. Depressant effect of carisoprodol upon reticulospinal facilitation (cat, 3.3 kg.; Nembutal, 25 mg./kg). The patellar reflex is elicited and recorded in A through D. A spinal facilitative site of the lateral region of the pons is stimulated during the periods indicated by the horizontal bars. Record A was obtained before the injection of carisoprodol. Record B was taken 2 min. after the injection of 10 mg./kg. of this compound. Between records B and C a second dose of carisoprodol, also 10 mg./kg., was injected. Record C shows block of facilitation 5 min. after the second injection of the drug. Record D shows recovery 90 min. after the first injection of carisoprodol. Time signal: 10 sec. and 1 min.

tween the dosages required in either instance can be accounted for on the basis of the different experimental conditions. The direct electric stimulation of the brain stem is likely to produce a massive and diffuse state of excitation of the reticular substance, instead of the more discrete and organized patterns of activity likely to occur in unstimulated animals. On the other hand, although decerebrate rigidity is obviously due to a change in the balance existing normally between facilitation and inhibition, it is not clear to what extent that equilibrium is disturbed in each individual preparation. It is conceivable that in most instances a slight shift in the opposite direction, such as the one due

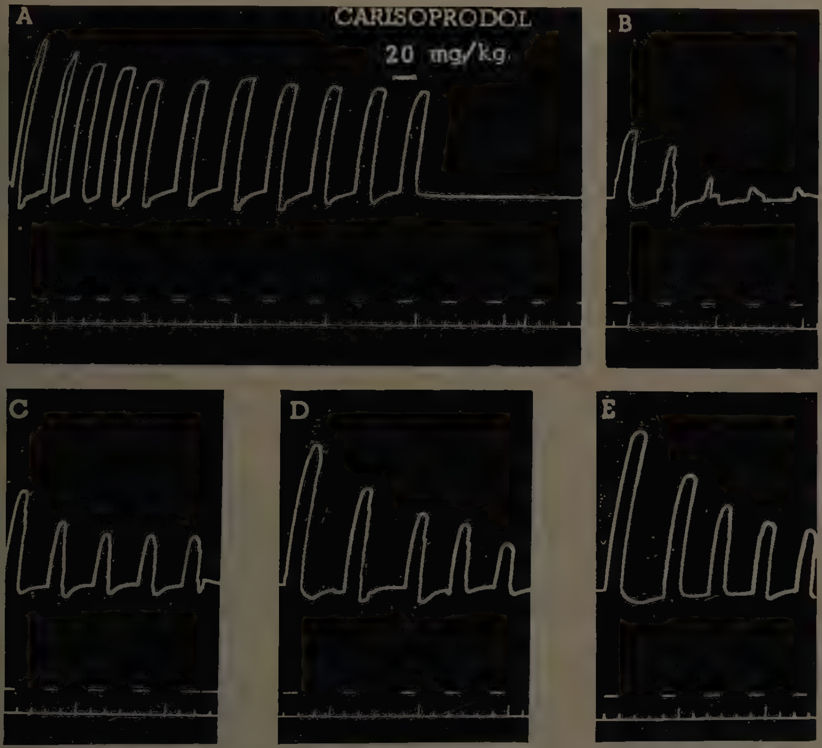

FIGURE 7. Effect of carisoprodol upon the increase in extensor tonus due to electric stimulation of the brain stem (cat, 2.3 kg., anesthetized with 25 mg./kg. of Nembutal). A site was found in the lateral region of the pons where the electric threshold for facilitation of the ipsilateral knee jerk was lower than usual (0.5 v., 100 cps, 1 msec. duration). If the voltage was increased above threshold value, the large tonic contractions of the quadriceps muscle were evoked. The horizontal bars indicate periods when the stimulation was switched on. Record A shows how repetitive stimulation of that site results in a gradual decrease in the strength of the contractions until a relatively steady level is reached. At the time indicated by the horizontal bar above the main record a dose of 20 mg./kg. of carisoprodol was injected. A sudden abolition of the effects of stimulation was observed. No signs of partial recovery were seen until about 30 min. later, when record B was taken. Although the first period of a series of stimulations resulted in a relatively large increase in tonus, successive periods gave rapidly decreasing responses. The course of recovery can be followed in records C, D, and E, taken 60, 90, and 120 min., respectively, after carisoprodol was injected. Time signal: 10 sec. and 1 min.

to small doses of carisoprodol, would be sufficient to restore the original balance and produce relaxation. Therefore, it was not surprising to see that the amounts of carisoprodol required to block the effects of direct electric stimulation were higher than those required to relax a decerebrate preparation.

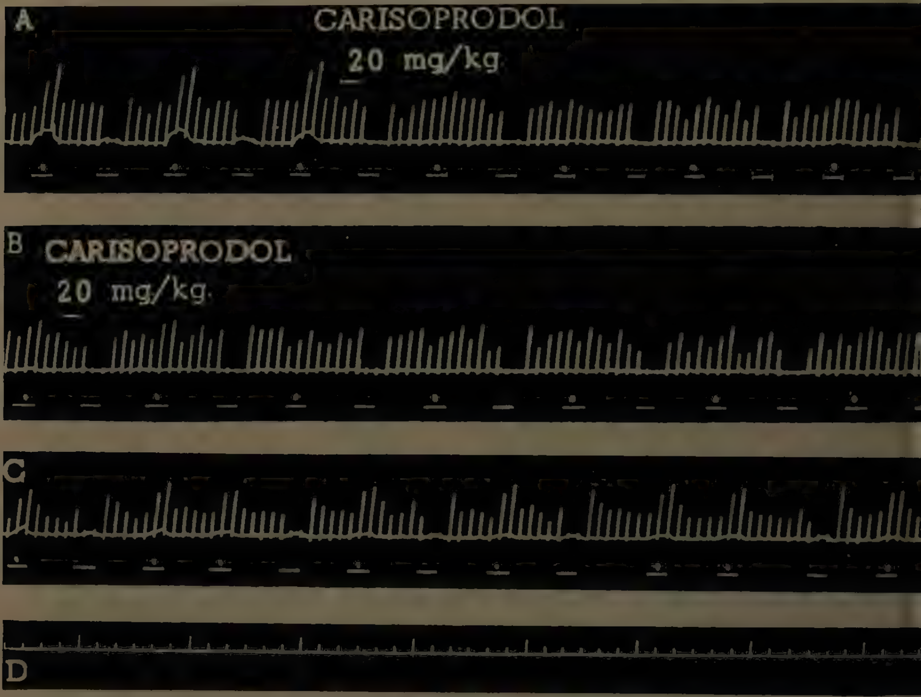

FIGURE 8. Effect of carisoprodol on the facilitation and inhibition of the patellar reflex elicited by electric stimulation of the brain stem (cat; Nembutal, 25 mg./kg.) Records A, B, and C: patellar reflex. Time signal: 10 sec. and 1 min. Two monopolar stimulating electrodes were implanted in the brain stem, one in the inhibitory midbulbar area, the other in a spinal facilitative site of the pons. Stimulation was applied through the electrodes during the periods indicated by the horizontal lines (—±—, facilitative; ——, inhibitory). Two doses of 20 mg./kg. of carisoprodol were injected as shown. Note how facilitation of the patellar reflex is rapidly abolished by the first injection, while inhibition is not affected even after the second dose. Record B is a continuation of A, whereas record C was taken 90 min. after the second injection, showing recovery of facilitation. In record C the periods of inhibition are followed by a facilitative rebound, absent while the drug was acting.

C. *Effect of Meprobamate upon Spinal Facilitation and Inhibition Elicited by Brain Stem Stimulation*

The fact that carisoprodol is a compound related closely to meprobamate and shares with it some pharmacological properties raised the question whether meprobamate would also act upon reticulospinal influences. Because a review of the literature failed to clarify this problem, experiments were conducted in which the methods and procedures already described were followed, but meprobamate instead of carisoprodol was used.

In one respect the results of both groups of experiments did agree: meprobamate failed to affect reticulospinal inhibition even with doses of up to 100 mg./kg.

The initial experiments created much confusion as to the influence of meprobamate upon reticulospinal facilitation. Whereas the effects obtained with carisoprodol were extremely clear-cut and consistent, the injection of meprobamate gave rise to a bewildering variety of results. In some experiments, for instance the one illustrated in FIGURE 9, the results obtained were similar to those obtained with carisoprodol; that is, meprobamate did block facilitation. In agreement with the observations of Berger (1954), we found that the effects of meprobamate developed rather slowly.

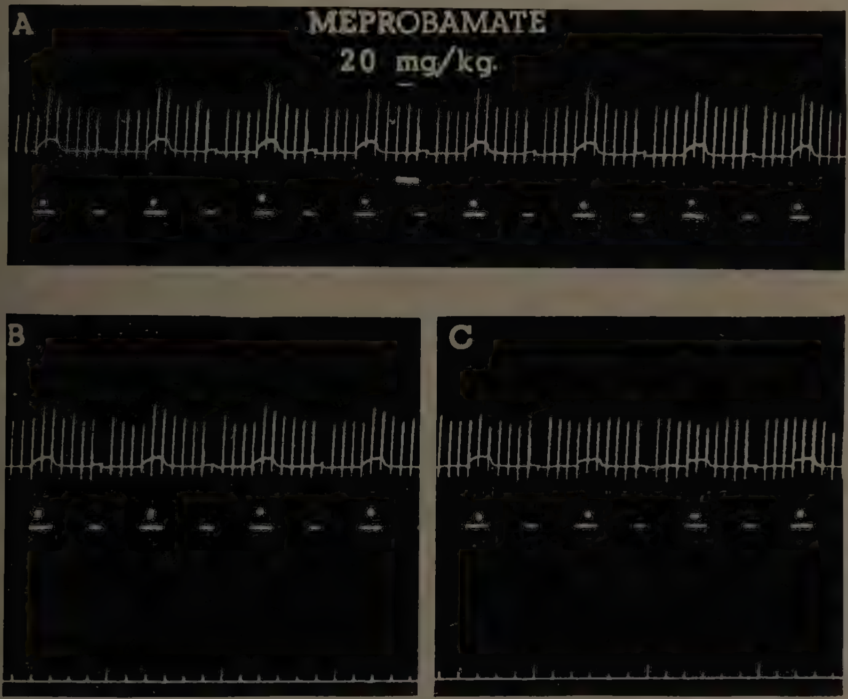

FIGURE 9. Effect of meprobamate upon spinal facilitation and inhibition elicited by electric stimulation of the brain stem (cat; Nembutal, 25 mg./kg.). Records A, B, and C show the changes produced in the patellar reflex by the stimulation of facilitative and inhibitory sites of the brain stem (facilitative stimulation, —•—; inhibitory stimulation, ———). In record A, 20 mg./kg. of meprobamate was injected. Records B and C were taken 10 and 20 min., respectively, after the injection of the drug. Record C shows that facilitation was blocked by the drug, whereas inhibition was not appreciably affected. Stimulation was maintained for about 1½ hours. No recovery was observed during this period. Time signal: 10 sec. and 1 min.

In other experiments, however, meprobamate did not interfere with reticulospinal facilitation, even if given at doses of up to 120 mg./kg. The only effect observed was a gradual decrease of the amplitude of the patellar reflex that nevertheless was enhanced during the periods of brain stem stimulation.

The confusion produced by these results was accentuated by the fact that completely different effects were often obtained in the same preparations. However, this eventually yielded a clue to the reason for such contradictory observations. It was observed that meprobamate produced a depression or block of reticulospinal facilitation only if injected within the first 2 or 3 hours

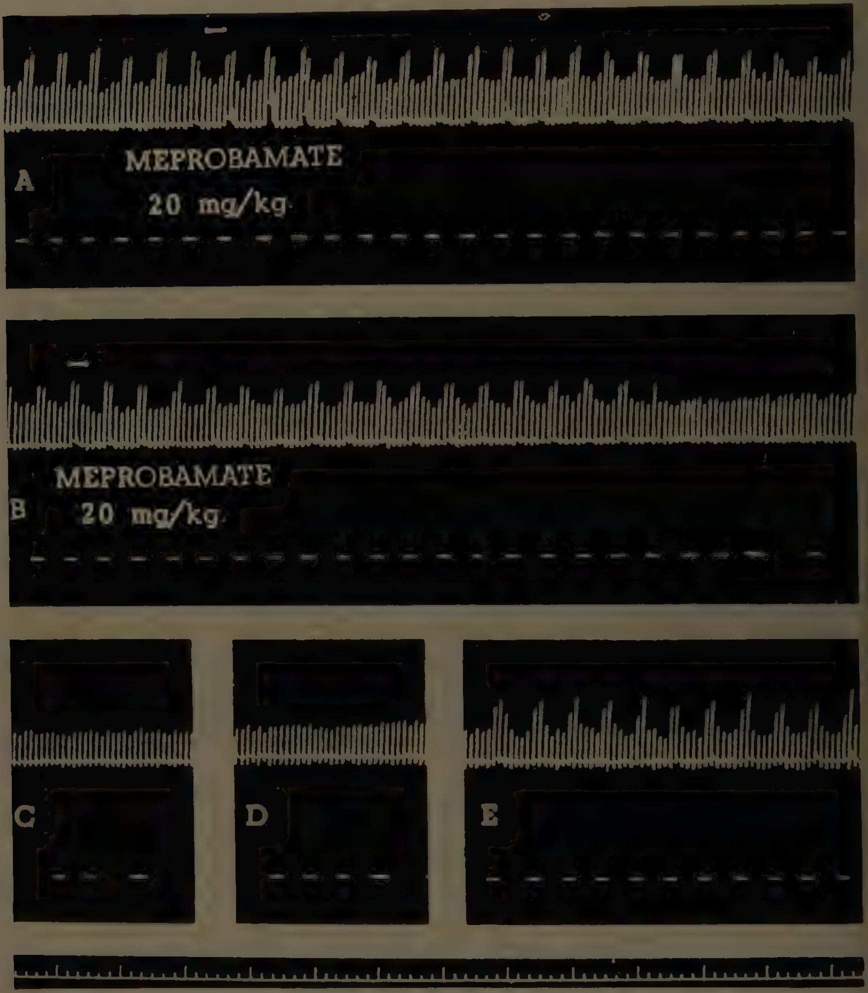

FIGURE 10. Influence of meprobamate on facilitation of the knee jerk elicited by stimulation of the brain stem (cat, 2.6 kg., anesthetized with 20 mg./kg. of Nembutal plus 15 mg./-kg. of Pentothal). *Top record:* patellar reflex which is facilitated at regular intervals, indicated by the horizontal bars, by repetitive stimulation of the brain stem. In record A, 20 mg./kg. of meprobamate was injected intravenously at the time indicated by the horizontal bar above the main record. Record B is a continuation of A. A second and equal dose of 20 mg./kg. was injected. About 10 min. after the second dose, facilitation was blocked. Record C was taken about one hour after the second injection of meprobamate, when the amplitude of the knee jerk reached a minimum. Record D was taken 80 min. after C, and record E shows recovery of facilitation that occurred approximately three hours after B. Time signal: 10 sec. and 1 min. This experiment was begun about 1 hour after the barbiturates were injected. A second test of the action of meprobamate in facilitation was carried out in this preparation. See FIGURE 11.

following the onset of barbiturate anesthesia. If a longer period was allowed to elapse, the effects of meprobamate became increasingly weaker until no depression of facilitation could be demonstrated, even with the higher dosages.

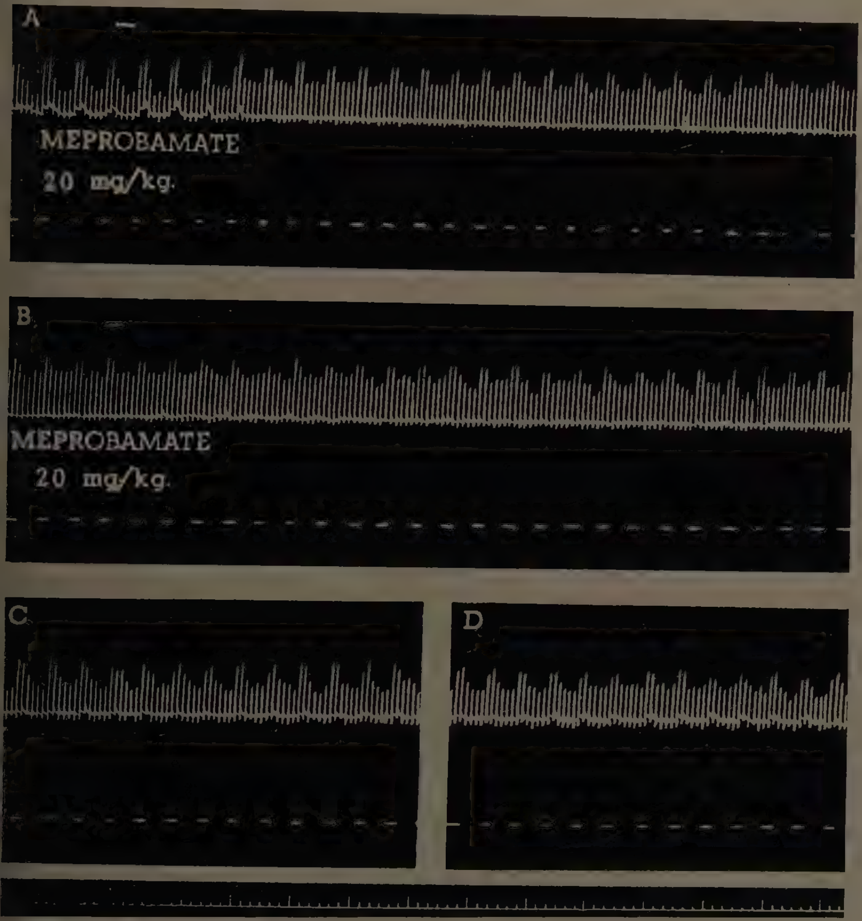

FIGURE 11. Effect of meprobamate upon reticulospinal facilitation. This figure is ac- ually a continuation of the experiment illustrated in FIGURE 10. Record E in FIGURE 10 ows how facilitation had recovered about 3 hours after the injection of a cumulative dose 40 mg./kg. of meprobamate. About 30 min. after this record a new dose of 20 mg./kg. meprobamate was injected in the same preparation, record A. In record B another 20 g./kg. of the same compound was injected, this time with no obvious effect on facilitation, though the amplitude of the patellar reflex is seen to increase. Record C was taken 30 in. after B. Meprobamate (10 mg./kg.) was injected between B and C, and another 10 g./kg. was given between C and D. A cumulative dose of 60 mg./kg. failed to block cilitation (*see text*). Time signal: 10 sec. and 1 min.

his is shown in FIGURES 10 and 11, which record two tests carried out in the me preparation with an interval of nearly 4 hours between tests.

It may be concluded from these experiments that meprobamate, although effective by itself upon reticulospinal facilitation, potentiates the depressant tion of Nembutal upon the reticular formation. Barbiturates exert a suppressing influence upon the spinal facilitative influences arising in the reticular formation, without affecting inhibition. One of the most critical factors in this type of experiment is, in fact, the dosage of Nembutal: it must be just sufficient to anesthetize the preparation without producing a complete paralysis of reticular activity.

These results cast some doubt, of course, on the conclusions derived from the experiments described in the preceding section. Although the results obtained with carisoprodol were extremely consistent, one cannot help wondering if the depression of reticulospinal facilitation produced by carisoprodol may not be due to a potentiating effect of that compound upon the barbiturate. It was considered advisable, therefore, to reinvestigate the action of carisoprodol on reticulospinal facilitation in decerebrate preparations.

D. Effects of the Electric Stimulation of the Brain Stem in Decerebrate Animals

In attempts to repeat the experiments described in *Section B* in decerebrate preparations, a number of difficulties were encountered. Some of these were purely technical. For instance, in the low (that is, intercollicular) decerebrate preparations, the regions of the pons that were usually stimulated to give rise to spinal facilitation were often damaged. If, in order to preserve the integrity of the pons, the transection of the brain stem is performed at higher levels, the result is usually a highly active preparation in which the effects of facilitative stimulation cannot always be separated from the background of spontaneous motor activities. Other difficulties, however, proved to be due to the existence of important differences in the processes elicited by stimulation in unanesthetized and Nembutalized preparations. In Nembutalized preparations the electric stimulation of facilitative sites momentarily enhances the patellar reflex. In decerebrate animals the same stimuli give rise to marked potentiations of that reflex which persist for relatively long periods after the applied stimulation is switched off. It seems advisable to give a detailed description of these differences which, in our opinion, have not been sufficiently emphasized in the literature.

Stimulation of facilitative areas in Nembutalized preparations. The different types of effects observed when the facilitative areas of the brain stem are stimulated under Nembutal anesthesia are summarized in FIGURE 12. Record A shows simple facilitation and inhibition of the patellar reflex. It is interesting to note that this record was obtained not with two separate stimulating electrodes, but actually with a single electrode, the position of which was not altered. The stimulating pulses employed to elicit both effects were of the same frequency, duration, and amplitude, but of opposite polarity. Facilitation was obtained with negative pulses and inhibition was observed if positive pulses were applied. This record demonstrates that antagonistic systems can be stimulated simultaneously, even with low stimulus intensities. In this instance the electrode tip was probably situated close to the inhibitory system of fibers or neurons that could be stimulated by an anode break. The facilitative system was further away and, although it was easily stimulated by the negative current, the membrane potential changes determined by the positive pulses were not strong enough to cause excitation. The effects of facilitation did predominate, masking those of inhibition.

In experiments designed to test the action of a drug upon the spinal effects of brain stem stimulation it is therefore necessary to determine, before injecting the drug, the homogeneity of the systems stimulated. In the course of this work we have found instances of facilitative effects being transformed, by the drug, into inhibitory ones. These observations, otherwise puzzling, can be explained on this basis and are irrelevant in the absence of definite information on the systems that were stimulated by the electrode.

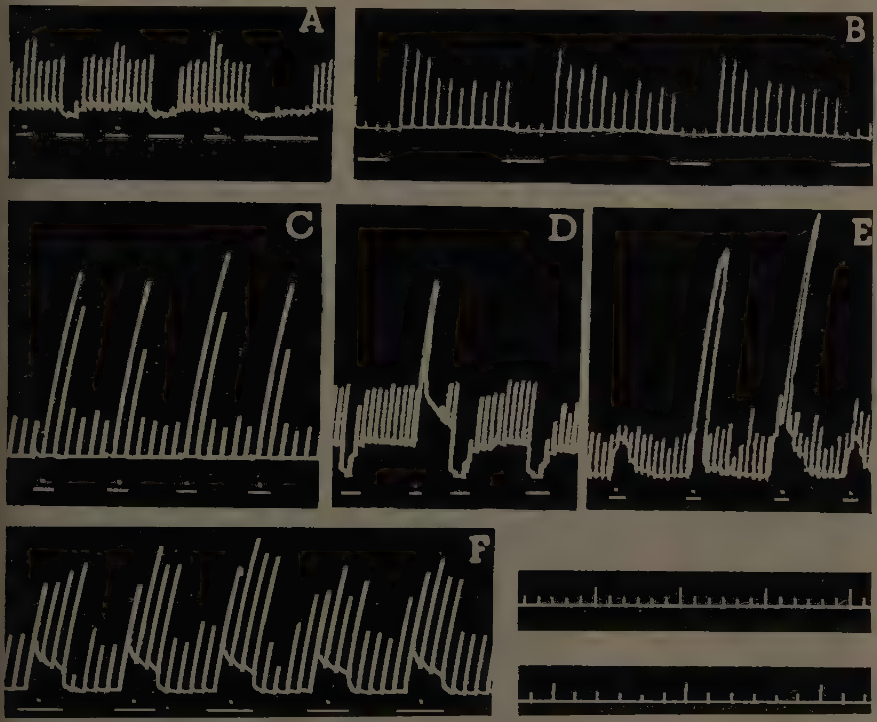

Figure 12. Main effects elicited in the patellar reflex and extensor tonus of Nembutalized animals by electric stimulation of the brain stem. The knee jerk and extensor tonus of the hind limb of cats anesthetized with Nembutal are shown in records A through F. In record A, facilitation (—•—) and inhibition (——) of the knee jerk are elicited with a single electrode merely by reversing the polarity of the stimulating pulses (*see text*). Record B shows inhibition and postinhibitory facilitation. Record C shows a large increase in the amplitude of the patellar reflex on facilitative stimulation, without simultaneous changes in extensor tonus. Records D and E, on the other hand, show large changes in tonus not accompanied by increase in the amplitude of the reflexes. Record F illustrates the most common result of facilitative stimulation: simultaneous changes in both the tonus and the amplitude of the reflex. Time signal: 10 sec. and 1 min. Upper scale applies to records A, D, and E; lower scale to records B, C, and F.

Record B of figure 12 shows how stimulation of the spinal inhibitory areas of the medulla may be followed by facilitation. This type of postinhibitory rebound is often seen in Nembutalized animals where the effects of stimulation of purely facilitative areas do not outlast the duration of the applied stimulation.

Two outstanding effects are observed upon stimulation of facilitative areas

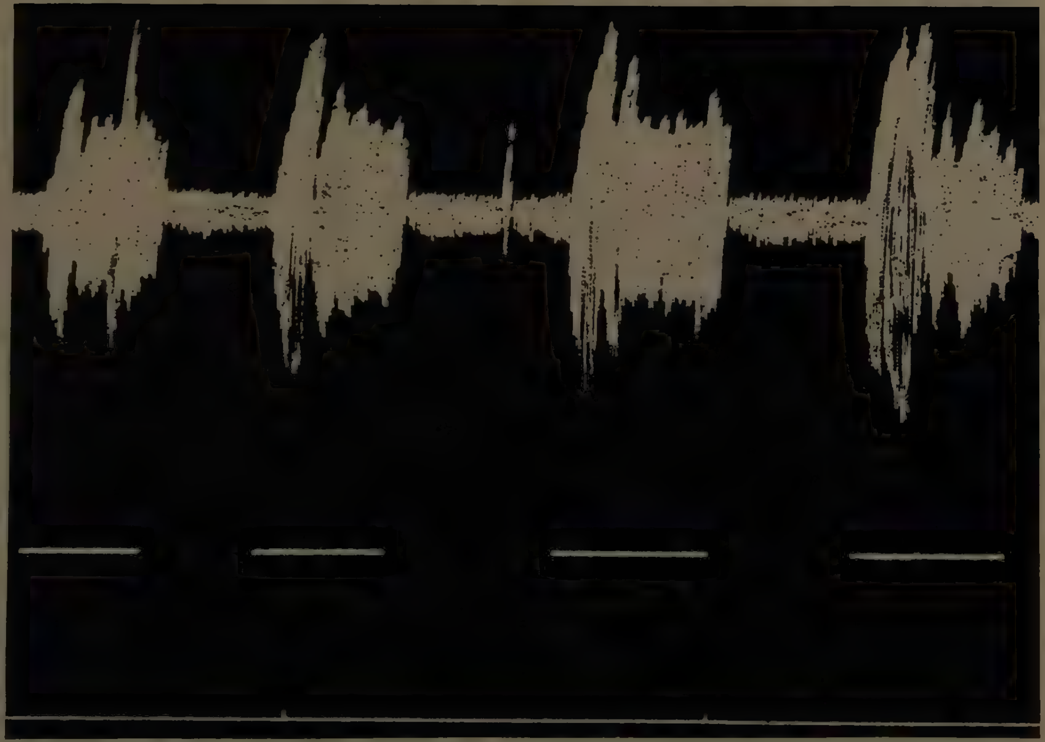

FIGURE 13. Effects of facilitative stimulation upon the amplitude of clonic movements of the hind limb of a preparation lightly anesthetized with Nembutal. This record shows how the stimulation of a lateral pontine facilitative site markedly increased the amplitude of the clonic movements exhibited by the leg of a lightly anesthetized cat. Between the second and third periods of stimulation a patellar reflex was elicited. Note how the amplitude of the clonic excursions of the limb decreases sharply as soon as stimulation stops. Time signal: 10 sec.

in Nembutalized preparations. In some sites (record C), an increment that may be very large, of the amplitude of the patellar reflex, is not accompanied by an appreciable simultaneous increase in the extensor tonus. In other sites of the brain stem such as in record D, changes in tonus only are produced. More frequently, however, facilitative stimulation results in a mixture of both effects. As a rule, the stimulus strength required to enhance the amplitude of the reflexes is lower than that required to cause an increase in the extensor tonus. In lightly anesthetized preparations showing a marked degree of tremor or clonus, stimulation of facilitative areas determines a marked increase in the amplitude of the clonic excursions of the limbs, which return promptly to the previous level as soon as the stimuli are discontinued (see FIGURE 13).

It must be emphasized that in Nembutalized preparations, all these effects can be elicited every 10 or 20 sec. for a period of hours without appreciable, observed change in either the efficiency of the stimulus or the amplitude of the patellar reflex between the periods of stimulation.

Stimulation of facilitative areas in unanesthetized preparations. In decerebrate preparations exhibiting marked spontaneous motor activity, the stimulation of facilitative areas of the brain stem increases the frequency and amplitude of those movements, but it is difficult to distinguish the effects actually due to the applied stimuli from the very "noisy" background.

In quiet decerebrate preparations that have been left undisturbed for some time, the initial stimulation of facilitative areas may give rise to any of the effects found in Nembutalized preparations, although a very important difference is soon discovered: each period of facilitation is followed by prolonged changes in the reflex excitability of the spinal cord that last many times longer than the applied stimuli. This is clearly seen in records A and B of FIGURE 14. These records were obtained during the preliminary exploratory stages of two of the experiments described in the next section. In record A, 3 different sites along an electrode track in the pons were stimulated. The 2 first sites proved to be inhibitory. However, at the third attempt, a volley of stimulating pulses lasting less than 4 sec. gave rise to a marked enhancement of extensor tonus followed by a marked, prolonged potentiation of the size of the patellar reflex. This reached a peak value about 1 min. after stimulation and lasted for another 3 min. In record B a similar effect is shown. This persistent enhancement in the reflex activity of the spinal cord produced by brain stem stimulation is a constant feature of experiments performed in decerebrate preparations. The word "facilitation" will be used henceforth in this paper to designate enhancement of spinal reflex activity occurring temporarily, during periods of stimulation. The prolonged changes that we have described will be referred to, for lack of a better term, as "postfacilitative activation" or more simply as "activation."

We are ignorant of the exact nature of this process. It is unknown whether it represents the persistence or afterdischarge of whatever type of electric activity is involved in the production of facilitation, or whether it is an entirely different phenomenon. In any event, the occurrence of activation in the decerebrate preparations is responsible for the temporal summation of the effects of consecutive periods of facilitative stimulation. This is shown clearly in FIGURE 15. When the stimulation is first applied (B), results similar to those ob-

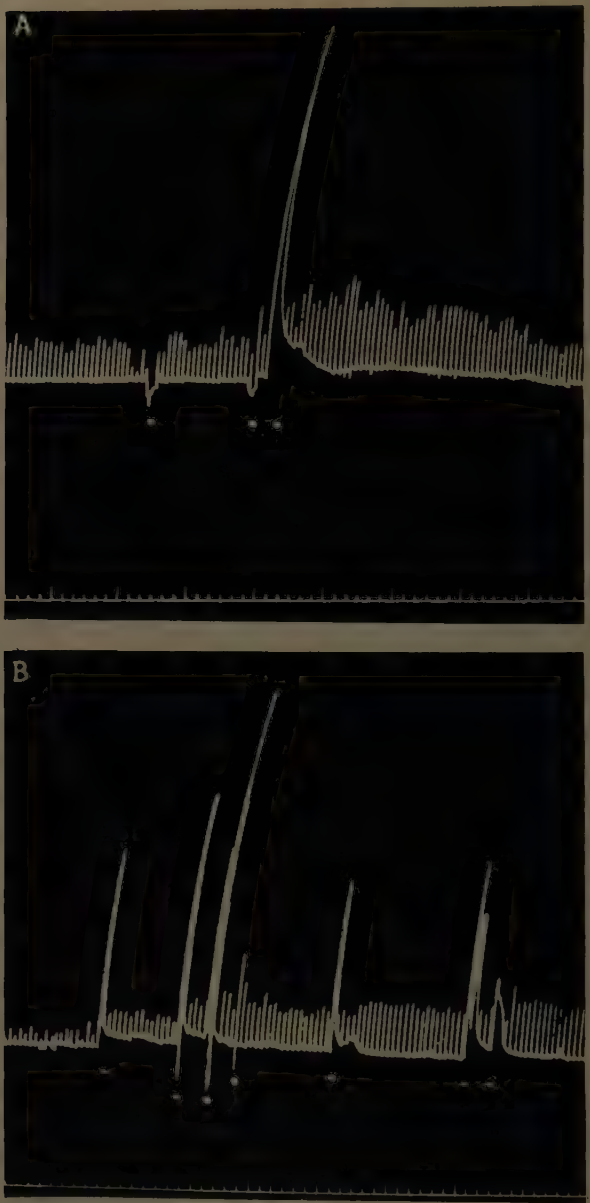

FIGURE 14. Spinal activation evoked by the electric stimulation of facilitative sites in the brain stem. Records A and B were taken during the initial exploratory stages in two separate experiments. The decerebrate preparations used in both experiments had been left undisturbed for long periods of time, and the amplitude of the reflex responses had diminished. Observe how the short periods of stimulation, indicated by dots, although lasting less than 4 sec. each, elicit marked and prolonged changes in the amplitude of the patellar reflexes. See text for further discussion of these effects. Time signal: 10 sec. and 1 min.

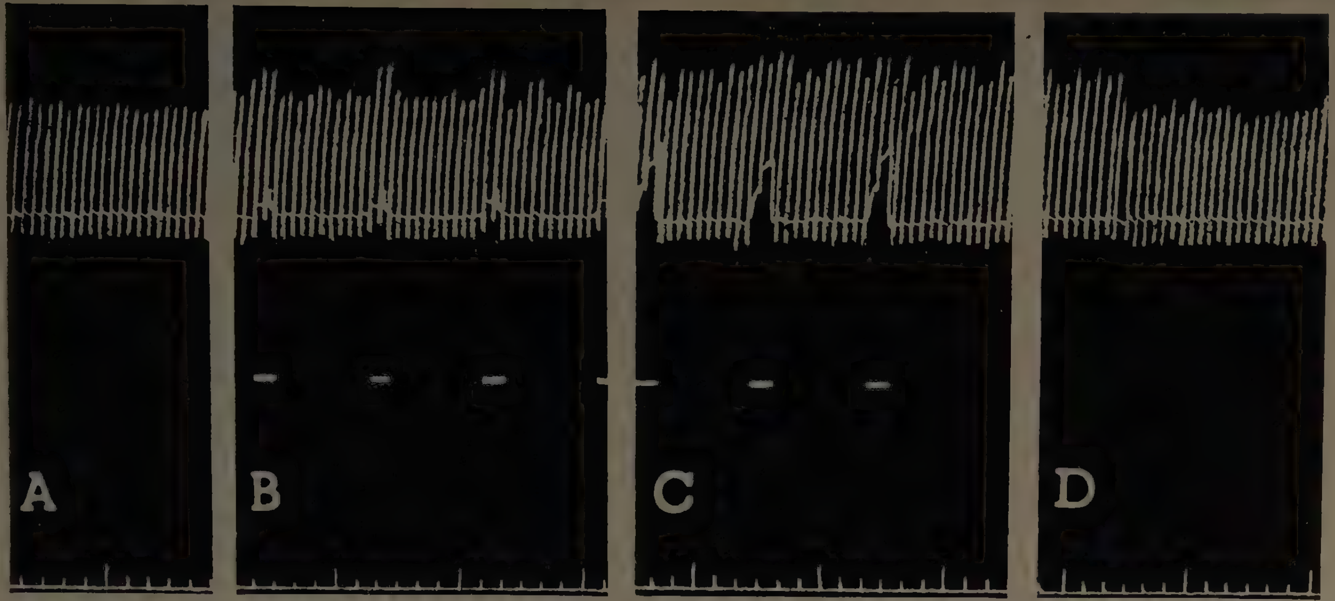

FIGURE 15. Spinal facilitation and activation due to the electric stimulation of the brain stem in a decerebrate preparation. Records A, B, C and D show the patellar reflex in a decerebrate cat and the changes produced by the electric stimulation of a facilitative site of the brain stem. Record A shows the amplitude of the patellar reflex after the preparation had been allowed to remain undisturbed for about one hour. Record B shows the effects of the first few periods of facilitative stimulation. Although the increases in the amplitude of the reflexes that occur *during* the periods of stimulation resemble those seen in Nembutalized preparations, the average size of the responses is higher than the level shown before stimulation, even in the intervals between the stimulation periods indicated by the horizontal bars. In record C, taken after about 5 min. of uninterrupted stimulation, the amplitude of the patellar reflex is permanently increased and the only noticeable immediate effect of stimulation is an increase in extensor tonus. Record D shows the disappearance of activation when stimulation ceases. The kymograph was stopped for 4 min. between the left and right portions of this record. Time signal: 10 sec. and 1 min.

tained in Nembutalized preparations are observed; that is, the amplitude of the patellar reflex increases *during* the periods of stimulation. However, the amplitude of the reflexes *between* the stimulation periods remains enhanced. In record C, 3 min. later, all the reflexes have attained the amplitude shown initially only by the facilitated ones. Record D shows how the amplitude of the activated reflexes is gradually reduced if stimulation is discontinued. An interval of 4 min. was allowed to elapse between the left and right portions of this record.

Summarizing these results, one may say that in the decerebrate preparations the direct effects of stimulating facilitative sites of the brain stem are followed, and often masked, by the development of persistent changes in the activity of monosynaptic reflex arcs; this development is referred to as spinal activation. These changes, occurring over a long period, can easily be summated, giving rise to a steady enhancement of spinal reflexes lasting as long as the stimulation applied to the brain stem at regular intervals is continued. Spinal activation is easily elicited in the decerebrate preparation, not only by direct electric stimulation of the brain stem but also, probably, by the intervention of the reticular formation, by any type of strong sensory stimuli. The main difficulty encountered in studying this phenomenon is in obtaining relaxed decerebrated preparations in which the onset of activation can be observed. Spinal activation, it should be added, can also be elicited in the periods of facilitation that follow bulbospinal inhibition.

Inhibitory effects in decerebrate preparations. The effects of electric stimulation in the spinal inhibitory areas of the medulla do not vary significantly between decerebrate and Nembutalized preparations, although the inhibitory effects are usually more obvious in the decerebrate, due to the existence of a more active background of motor activity. It is interesting to note that inhibition has not outlasted stimulation in our experiments, although post-inhibitory facilitation has been observed.

E. Effects of Carisoprodol and Meprobamate on Spinal Facilitation and Activation in Decerebrate Preparations

We have performed experiments in decerebrate preparations similar to those described in *Section B* for animals anesthetized with Nembutal. Repeated stimulation of the facilitative regions of the brain stem in the decerebrate animal causes, as we have indicated, a gradual potentiation or activation of spinal reflexes which builds up at a variable rate to a steady value. When this steady level was attained, carisoprodol was injected.

It was rather surprising to find in these experiments that the action of carisoprodol upon decerebrate, unanesthetized preparations is actually much more intense than that shown in Nembutalized animals. The process of activation is promptly abolished by 3 to 5 mg./kg. of carisoprodol, and the amplitude of the patellar reflexes is reduced to the levels shown before stimulation was initiated. The direct effects of brain stem stimulation upon the knee jerk, that is, facilitation, is also blocked or greatly reduced.

These effects are illustrated in FIGURE 16. The record in the insert labeled A was obtained at the beginning of the experiment when the first facilitative stimuli were applied to the brain stem. It may be seen that after a few periods

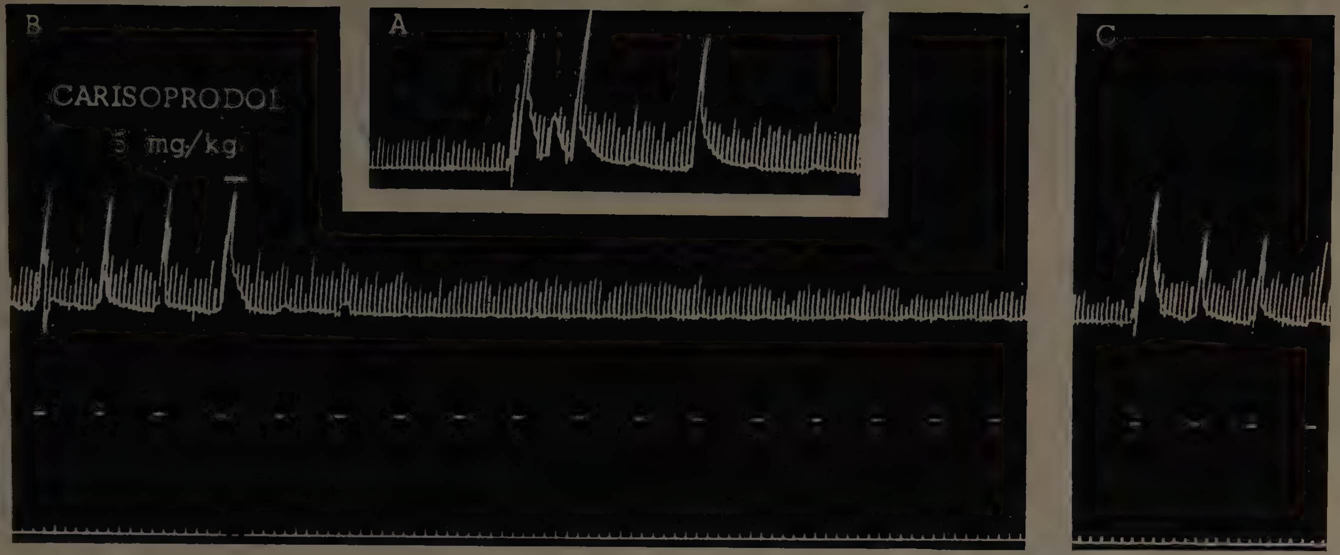

Figure 16. Effect of carisoprodol upon spinal facilitation and activation evoked by the stimulation of the brain stem in a decerebrate preparation. Insert A shows the activation produced by the first few periods of stimulation of a facilitative site in the brain stem of a decerebrate cat. The amplitude of the patellar reflex, which is recorded in A, B, and C, is seen to increase by a factor of nearly 2 as soon as a facilitative site of the brain stem was stimulated. At the beginning of record B large facilitative effects can be seen, consisting mainly of an increase in extensor tonus. The level of activation, that is, the persistent increase in the amplitude of the reflex responses between the stimulation periods, is constant. The injection of 5 mg./kg. of carisoprodol at the time indicated by the bar is followed by a rapid abolition of activation and a block of facilitation. Record C shows recovery approximately 70 min. after the injection of the drug. Time signal: 10 sec. and 1 min.

of stimulation the amplitude of the patellar reflexes was increased until it reached a fairly steady value between the stimulation periods. At the beginning of record B, taken a few minutes later, both facilitation and marked activation may be observed. The injection of 5 mg./kg. of carisoprodol produced not only a facilitation block, but also a decrease in the amplitude of the reflexes to the level prior to stimulation. A similar experiment showing the three main effects of brain stem stimulation—inhibition, facilitation, and activation—is illustrated in FIGURE 17. In this instance, spinal activation was evoked by repeated postinhibitory facilitation, the stimulating electrode being implanted in the medial region of the medulla. It can be seen that each period of inhibition is followed by a facilitation that in turn gives rise to a persistent enhancement of the patellar reflex. The amplitude of this reflex is seen to increase stepwise until a steady level is reached. Both facilitation and activation were abolished by 3 mg./kg. of carisoprodol, whereas inhibition remained unaltered.

Although activation is consistently abolished by small amounts of carisoprodol, great differences are observed among individual preparations as regards the exact amount of carisoprodol necessary to produce a complete block of reticulospinal facilitation, in contrast to the more uniform effects observed in Nembutalized animals. In some experiments, as in that shown in FIGURE 17, facilitation has been abolished by 3 mg./kg. of carisoprodol; in other instances larger amounts, 10 to 15 mg./kg., is required; a small residual fraction of facilitation, resisting amounts of carisoprodol up to 50 mg./kg., has been observed in one animal (see FIGURE 18). In this instance, however, activation and the greatest part of facilitation were abolished by the dose of 10 mg./kg. initially injected.

In FIGURE 19 another example of the actions of carisoprodol upon facilitation and activation is shown. The records in the upper row show, respectively, facilitation upon a background of steady activation (A), and its waning when facilitative stimulation is discontinued (records B and C). Between records C and D stimulation was resumed and activation developed once more. Between records D and E, 10 mg./kg. of carisoprodol was injected. In record E the average amplitude of the reflex responses is smaller, but some facilitation can still be observed. In F, facilitation has been abolished, and the amplitude of the knee jerk is even lower than in C. Record G shows recovery 60 min. later.

FIGURE 20 shows the effect of carisoprodol in a highly active decerebrate preparation with a high degree of muscle tonus and frequent spontaneous movements, which are increased during facilitative stimulation.

Experiments performed with meprobamate under the same experimental conditions reveal the existence of two profound differences between that compound and carisoprodol. In the first place there is a marked quantitative difference: meprobamate, like carisoprodol, does suppress activation, but the amounts required to do so are much larger, 20 to 30 mg./kg. being required. This dose is of the same order as those shown by Berger *et al.* (1959) to be necessary to abolish decerebrate rigidity. The second difference is qualitative: meprobamate does not affect facilitation in the unanesthetized preparations. Even if large amounts of meprobamate are given until the amplitude of the patellar reflex is greatly reduced, one finds that the stimulation of facilitative sites always results in a clear and definite facilitation of the reflex responses that can

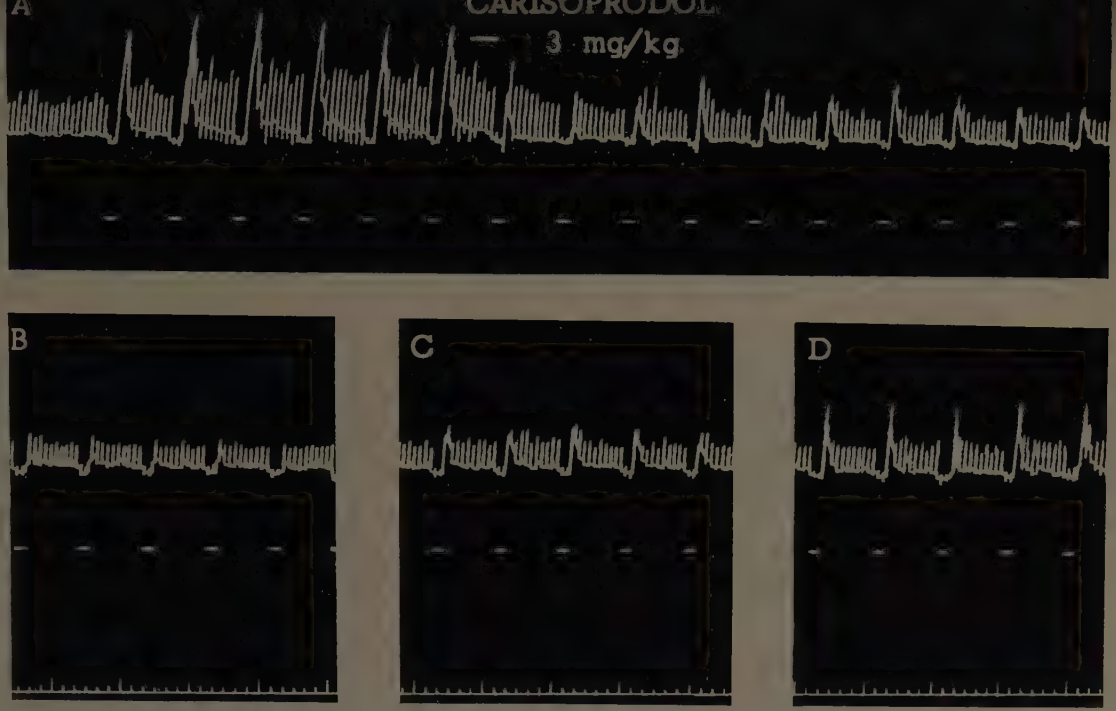

Figure 17. Effects of carisoprodol upon spinal facilitation and activation elicited by stimulation of a medullary inhibitory site. In records A through D the patellar reflex is elicited. At regular intervals during the periods indicated by the horizontal bars an inhibitory site of the medial region of the medulla was stimulated. The inhibition of the knee jerk was followed by a marked increase in extensor tonus and activation of the reflex responses. The average amplitude of the patellar reflex is seen to increase stepwise when the stimulus is applied and repeated until a steady level is reached. The injection of 3 mg./kg. of carisoprodol resulted, as indicated, in an abolition of both postinhibitory facilitation and activation. Maximum effect of the drug is seen in record B taken about 10 min. after the injection. Records C and D, taken 40 and 60 min. after the injection, show recovery. Time signal: 10 sec. and 1 min.

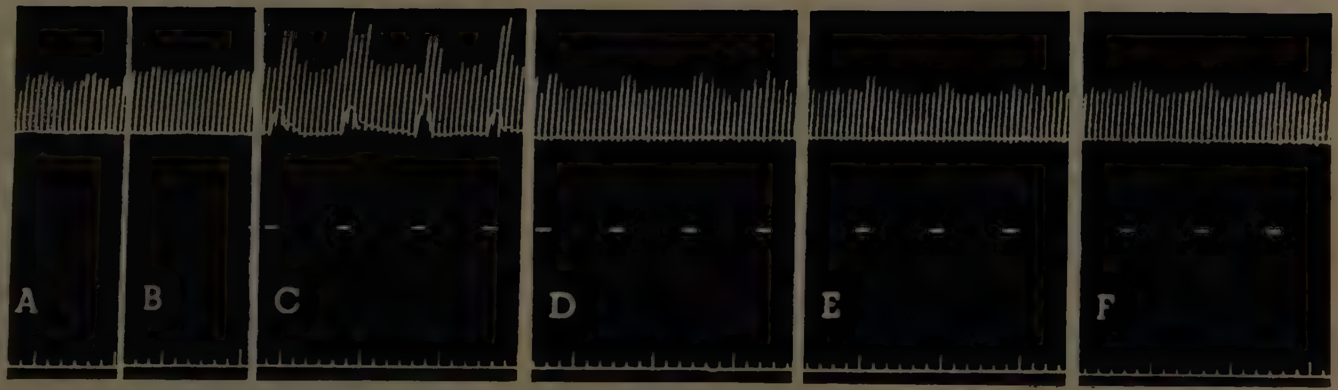

FIGURE 18. Effect of carisoprodol on spinal facilitation and activation elicited by electric stimulation of the brain stem. Record A shows the amplitude of the knee jerk before the exploratory stimulation of the brain stem was attempted. Between records A and B a facilitative site was found. A few periods of stimulation resulted in an appreciable increase in the amplitude of the knee jerk. Record C shows the effects of stimulation of that site during periods indicated by the horizontal lines. Observe the occurrence of both facilitation (that is, an increase in both the amplitude of the reflex and the level of muscle tonus) and activation (*see text*) in the intervals between the stimulation periods. Between C and D, 10 mg./kg. of carisoprodol was injected. Record D was taken 10 min. after the injection of carisoprodol. Activation is abolished and facilitation greatly reduced. The residual facilitation observed in record D could not be abolished by the injection of an additional dose of 40 mg./kg. of carisoprodol given in two 20-mg./kg. injections between records D and E, and E and F, respectively.

be followed until the knee jerk is almost completely abolished. This is illustrated by FIGURES 21 and 22.

DISCUSSION

The exploratory character of the work described should be emphasized again here. It will be evident, from a brief inspection of the contents of this paper,

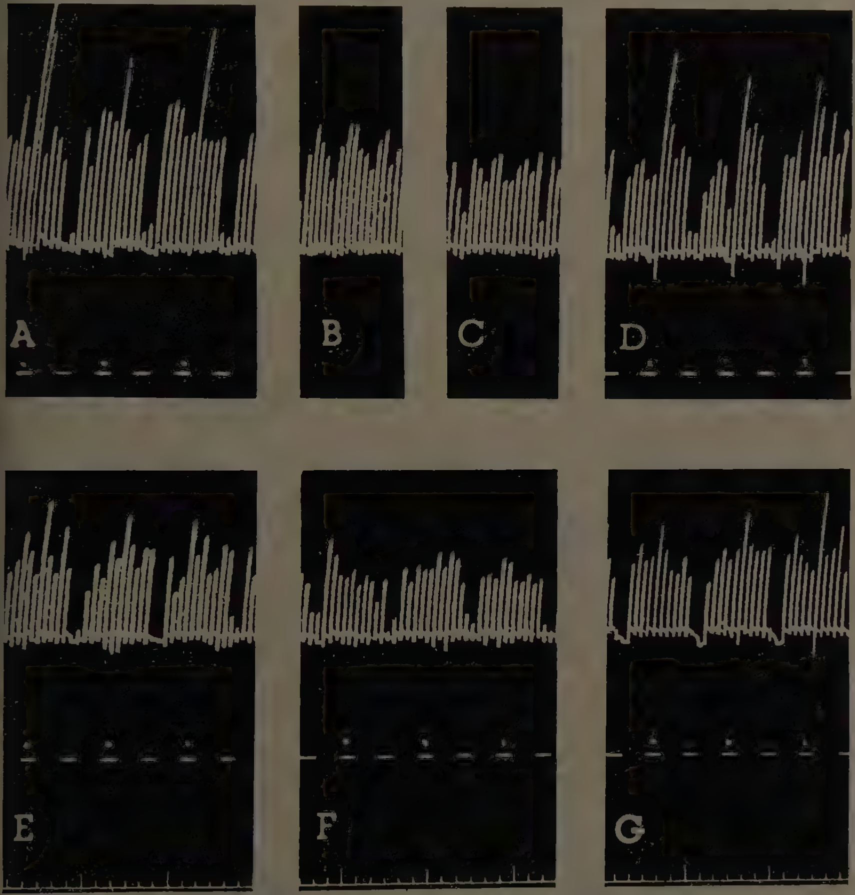

FIGURE 19. Influence of carisoprodol on spinal facilitation and activation in a decerebrate preparation. In records A through G the patellar reflex of a decerebrate cat was recorded. Reflex excitability of the spinal cord was good and the amplitude of the responses was irregular. Record A shows the effects of stimulation of facilitative (—•—) and inhibitory (——) sites. Record B was taken 2 min. after the stimulation of the brain stem had been discontinued. Record C was taken 8 min. after B, still in the absence of stimulation. Note how the amplitude of the reflexes has decreased. Just before record D, stimulation was renewed. Just after D, 10 mg./kg. of carisoprodol was injected. Record E was taken 10 min. after the injection of the drug. Note how, in spite of the continued intermittent stimulation, the average amplitude of the reflex responses has decreased. A new dose of 5 mg./kg. of carisoprodol was injected after E, and F was taken 10 min. after this second injection. Notice how facilitation has been abolished and that the size of the reflex responses is even lower than in C. Inhibition is not affected by the drug. G shows recovery 60 min. after the administration of the second injection. Time signal: 10 sec. and 1 min.

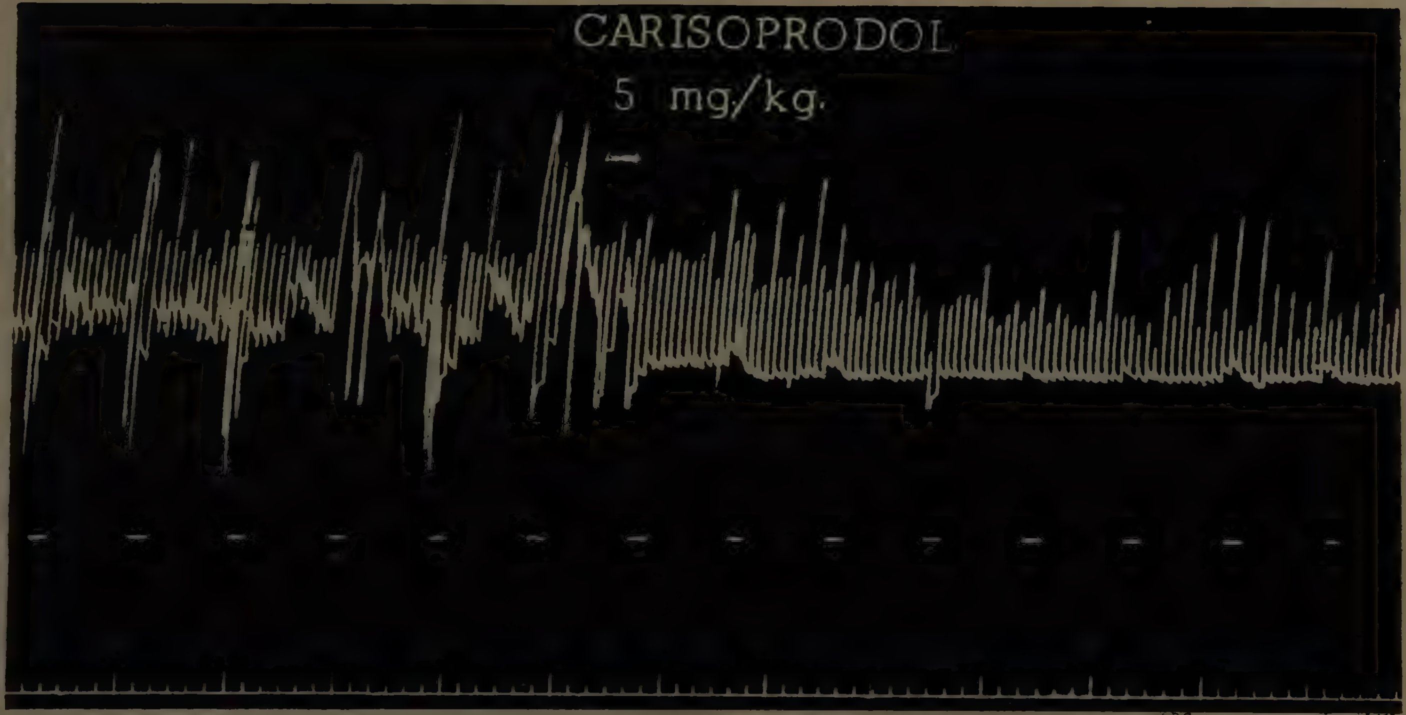

Figure 20. Effect of carisoprodol upon extensor tonus, facilitation of the knee jerk and spontaneous activity in a decerebrate preparation. The knee jerk is elicited at regular intervals throughout this record. The stimulation of a lateral pontine facilitative site during the periods indicated by the horizontal bars resulted not only in an increased amplitude of the reflex response, but also in marked movements of the limb and changes in the tonus. All these effects were markedly decreased after the injection of 5 mg./kg. of carisoprodol. The effects of the injection of the drug persisted in this experiment for about 45 min. Time signal: 10 sec. and 1 min.

that a number of important and obvious tests have not been performed. Further advance toward an understanding of the mechanism of action of carisoprodol must necessarily include an investigation of the effects of this compound on several processes, such as the differential action of reticular facilitation upon large and small motoneurones and the electric activity of the reticular formation, including potentials evoked by the stimulation of peripheral sense organs. Work is already in progress on some of these problems.

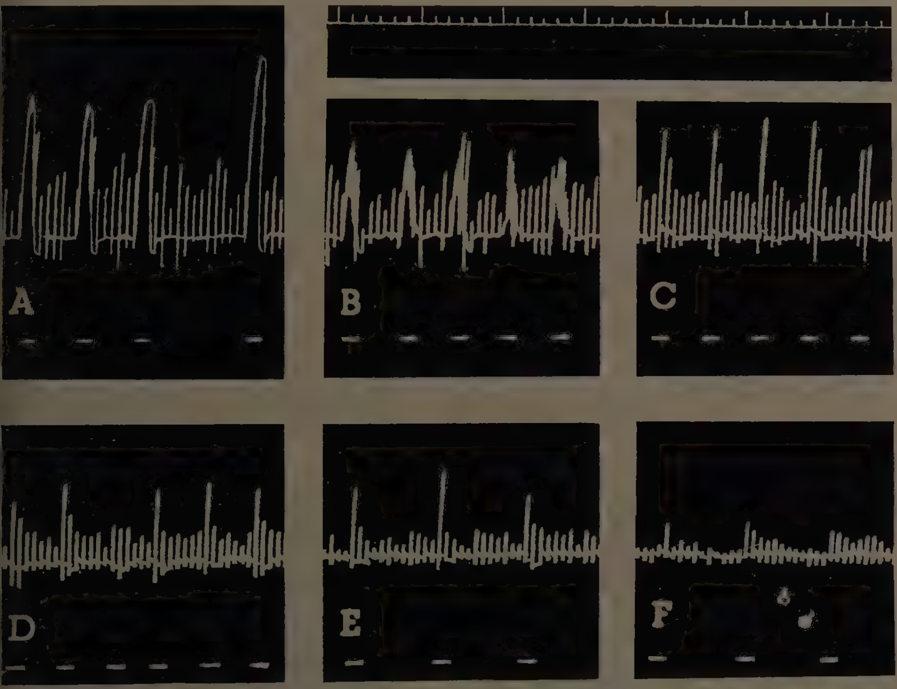

FIGURE 21. Effects of meprobamate upon reticulospinal facilitation and activation in a decerebrate animal. A through F: patellar reflex. A facilitative site of the brain stem was stimulated during the periods indicated by the horizontal bars. In A, before the injection of the drug, facilitative stimulation elicits large enhancements in extensor tonus. After A, a cumulative dose of 60 mg./kg. of meprobamate was injected in about 40 min. Between A and B, the first 20 mg./kg. was given. The size of the reflexes is slightly reduced, and clonic movements are now elicited by brain stem stimulation. Between B and C, a second dose of 20 mg./kg. was injected. The effect of facilitative stimulation now resembles that often found in Nembutalized preparations. Between C and D, a third and final dose of 20 mg./kg. of meprobamate was injected. Record F, taken 45 min. after injection of the first dose of the drug, shows that, although the amplitude of the reflex responses is now greatly diminished, facilitative effects are still very marked. Time signal: 10 sec. and 1 min.

The most interesting conclusion drawn from the experiments thus far completed is the conviction that carisoprodol represents not only a useful clinical weapon for combating muscle spasm and associated pain, but also a new tool in physiological research. As we have seen, carisoprodol can be used to interfere with some of the central nervous mechanisms involved in the production and control of muscle tonus, giving us an opportunity to learn more about them.

The results obtained from the study of the actions of carisoprodol on reticulospinal influences have shown that if we desire to describe accurately the results of brain stem stimulation in decerebrate preparations, the concept of reticulospinal facilitation must be complemented with that of postfacilitative activation, a term that we have used in this paper to designate the prolonged increase in the amplitude of spinal reflexes elicited by facilitative stimulation. Activation may outlast the duration of the applied stimulating volleys by at least two orders of magnitude.

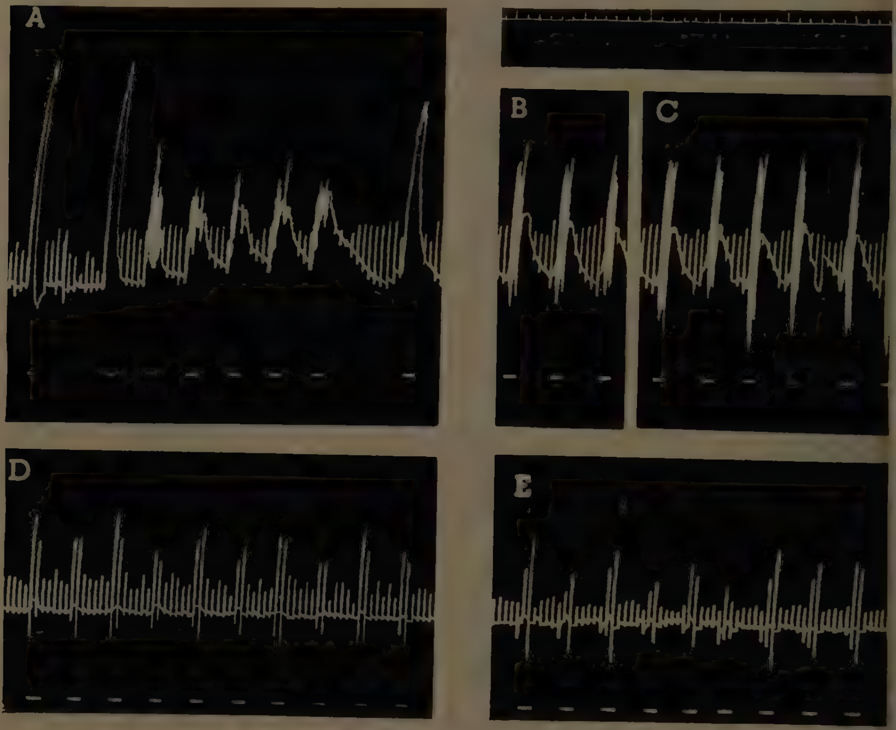

FIGURE 22. Effects of meprobamate upon reticulospinal activation in a decerebrate preparation. A through E: patellar reflex. A facilitative site in the brain stem was stimulated during the periods indicated by the horizontal bars. In A, before injection of the drug, facilitative stimulation results in an enhancement of muscle tonus and some clonic movements. Between A and B, 30 mg./kg. of meprobamate was injected. B was taken 10 min. and C 20 min. after the injection. Note how facilitative stimulation now gives rise to marked clonic movements rather than to an increase in tonus. Another dose of 20 mg./kg. of meprobamate was injected between C and D and an additional 10 mg./kg. between D and E. A marked facilitation of the greatly reduced knee jerk, similar to that seen in FIGURE 21, is observed even after this cumulative dose of 60 mg./kg. Time signal: 10 sec. and 1 min.

We are completely ignorant not only of the nature of activation, but even of the level of the neuroaxis where it takes place. We do not know whether activation depends upon the persistence of the excitatory processes elicited in the reticular formation by the electric stimulation of facilitative sites, or whether it might be a purely spinal process, such as a change in the "setting" or level of activity of spinal servomechanisms produced by reticular influences. In any event, we are tempted to assume that activation plays a very important role in the genesis of decerebrate rigidity and, possibly, of spastic clinical conditions.

In decerebrate preparations that have relaxed spontaneously, that is, in the absence of strong sensory stimulation, one can easily demonstrate how the restoration of rigidity by brain stem stimulation depends upon the temporal summation of successive activation elicited by each period of stimulation. On the other hand, although the stimulation of facilitative sites in Nembutalized preparations may result in large increases in the muscle tonus or amplitude of spinal monosynaptic reflexes, these changes are never followed by lasting modifications in the level of spinal reflex activity.

It is interesting to compare the effects of three drugs used in this investigation—Nembutal, meprobamate, and carisoprodol—upon the two processes of facilitation and activation. These results indicate that facilitation and activation may be considered different events from the point of view of drug action.

Nembutal and other barbiturates, and general anesthetics as well, exert a depressant influence on both spinal facilitation and activation. The dose needed to suppress activation is lower, however, than that required to block facilitation. In our experience, for instance, large facilitative effects but no activation can be elicited in preparations anesthetized with 25 mg./kg. of Nembutal. The injection of an additional 5 or 10 mg./kg. of that compound results in a block of facilitation.

Meprobamate in doses of 20 to 30 mg./kg. also blocks spinal activation. These amounts are of the same order as those shown by Berger *et al.* (1959) to be necessary to abolish decerebrate rigidity. Although, as we have seen, the depressant action of Nembutal on the reticular formation can be potentiated by this compound, facilitation is *not* abolished by meprobamate even if injected in amounts of up to 120 mg./kg.

Finally, carisoprodol has been shown to possess a strong depressant action on both facilitation and activation. Activation is usually abolished by small doses of this drug, 3 to 5 mg./kg. These low dosages are also sufficient to block facilitation in many experiments, although in some cases higher doses, 10 to 15 mg./kg., are required. In one instance, illustrated in FIGURE 18, a small fraction of facilitation was seen to remain even after injection of 50 mg./kg. of the drug. We feel it is likely that those differences may be related to the anatomical location of the sites stimulated in each experiment. This, of course, could be proved only by systematically correlating the effects of the drug with the exact position of the electrode used to elicit facilitation.

In the course of experiments now in progress related to the effects of carisoprodol on the electric activity of the reticular formation, we have observed some differential effects of this compound upon spinal facilitation elicited by stimulating alternately several sites in the same side of the brain stem of a preparation. In general, we find that facilitative effects elicited from more caudal sites are more resistant to the action of the drug. This suggests that the action of carisoprodol may be more pronounced upon the excitatory processes taking place in the reticular substance than upon the conduction or transmission of the activity elicited by these processes in reticulospinal pathways.

These observations may also help to account for the puzzling quantitative difference observed between the actions of carisoprodol on decerebrate and Nembutalized preparations. As barbiturates by themselves exert a depressant action upon reticular activity, one would expect that the doses of carisoprodol required to depress facilitation should be smaller in the Nembutalized animals. However, in decerebrate preparations, facilitation is often blocked by 3 mg./kg. of carisoprodol, while in Nembutalized animals a dose about 5 times as large or more of this compound is needed to produce the same effect. It is likely that in decerebrate preparations facilitation may be obtained by the stimulation of sites linked to the terminal reticulospinal systems of fibers by indirect pathways containing more synaptic relays. Therefore, as Barany (1947) pointed out, these would be more vulnerable to the action of both Nembutal and carisoprodol. In the Nembutalized preparations, where facilitative sites are certainly more difficult to discover, facilitation may be obtained only if regions more directly connected to terminal pathways are stimulated. These effects should be more resistant to drug action.

One may conclude from these experiments that carisoprodol exerts upon the facilitative effects of brain stem stimulation an action roughly similar to that produced by barbiturates and general anesthetics. This action, however, is apparent with very low doses and is not accompanied by changes in behavior or level of consciousness.

The effects of carisoprodol upon the central nervous system seem to be more selective than those produced by the central muscle relaxants known generically as interneuron blocking agents. Because of the specific depressant action of this compound upon reticulospinal facilitation and activation, it seems reasonable to regard carisoprodol as a new type of muscle relaxant. Also, in view of the results described in this paper and those obtained by Berger *et al.* (1959), carisoprodol may be characterized as a general depressant agent of the activating influences, both ascending and descending, originating at the reticular formation of the brain stem.

Although carisoprodol is a rather powerful antagonist of the potentiating effect of eserine on spinal monosynaptic reflexes, it is doubtful that this effect may be due to the atropinelike action that carisoprodol is known to exert on some areas of the central nervous system. In the first place, as Schweitzer and Wright (1937) indicated, the potentiating effect of eserine on spinal reflexes is not likely to be due to an increase in the effect of the acetylcholine that may be released in central synapses. Acetylcholine, in fact, has a depressant influence on the same reflexes that are potentiated by eserine. On the other hand, as those authors demonstrated and as we have confirmed in this work, atropine does not antagonize the effects of eserine on the spinal cord.

One of the most important pharmacological actions of carisoprodol, from the viewpoint of its therapeutic applications, is its selective analgesic action upon pain originating in skeletal muscle, bones, and joints, particularly if it is accompanied by exaggerated muscle tension. Our observations do not bear directly upon the mechanism of this analgesic action. One wonders, however, whether the pain associated with increased muscle tonus might not be due to a self-regenerative or self-sustaining process in which the muscle spasm may represent an important link.

We know that sensory information is transmitted to the brain cortex not only along the classic lemniscal systems, but also through slower pathways, involving longer latencies, that form an integral part of the reticular formation. The effects of peripheral stimulation in the decerebrate preparation show that sensory impulses act upon muscle tonus, partly, perhaps, through the intervention of the reticular formation. It is conceivable that in lesions of the locomotor apparatus a similar process may give rise to an increase in tonus in the muscle masses surrounding injured sites. This increased muscle tonus may lead to increased afferent discharges, and a self-sustained process is thus initiated. The action that carisoprodol would have on such a system is obvious from the results of this work. This is, admittedly, only a hypothesis, but one that may easily be used to design new experiments.

Summary and Conclusions

The effects of carisoprodol upon spinal reflexes and the facilitation and inhibition of those reflexes elicited by the electric stimulation of the brain stem reticular formation have been investigated in cats.

Small amounts of carisoprodol, 3 to 5 mg./kg., are very effective in abolishing rigidity in decerebrate animals, but have only a variable and relatively weak action on the spinal reflexes.

Although carisoprodol behaves as a weak antagonist of the potentiating effect of strychnine upon spinal polysynaptic reflexes, it markedly antagonizes the potentiating effect of eserine on spinal monosynaptic reflexes.

In contrast with other central muscle relaxant agents, such as mephenesin, that depress *both* spinal facilitation and inhibition due to brain stem stimulation, carisoprodol exerts a specific suppressing action upon reticulospinal facilitation. Bulbospinal inhibition is not affected by as much as 70 mg./kg. of the drug. In Nembutalized preparations a marked depression of reticulospinal facilitation is observed with 10 mg./kg. of carisoprodol. Complete blocking requires 15 to 20 mg./kg.

The effects of stimulating brain stem facilitative sites in decerebrate preparations were so different from those obtained in anesthetized animals that a detailed description of these differences is included in this paper. Whereas in Nembutalized animals, stimulation of the brain stem results in an enhancement or facilitation of spinal monosynaptic reflexes only during stimulation, in decerebrate preparations facilitation is followed by potentiation of the patellar reflex that persists for relatively long periods. This has been called spinal activation.

The effect of carisoprodol on facilitation and activation was tested in decerebrate preparations, where this drug has proved to have a much more marked action than in Nembutalized animals. Three to five mg./kg. are usually sufficient to abolish activation. Facilitation is greatly depressed and, in some instances, completely blocked by these small doses.

The effect of meprobamate upon reticulospinal influences was also studied. In decerebrate animals this compound affects neither facilitation nor inhibition, although it abolishes activation at doses of about 20 to 30 mg./kg. In Nembutalized preparations, however, meprobamate potentiates the depressant action of the barbiturate upon the reticular formation, and facilitation is blocked by doses that seem to vary with the blood level of the anesthetic.

In view of these results and those obtained by other investigators, carisoprodol may be characterized as a depressant agent for a large fraction of the activating and facilitating influences, both ascending and descending, that originate at the reticular formation of the brain stem. As far as the selective action of carisoprodol upon reticulospinal facilitation is concerned, it seems reasonable to regard this compound as a new type of muscle relaxant.

ACKNOWLEDGMENTS

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REFERENCES

BARANY, E. H. 1947. A theoretical note concerning the action of drugs on the central nervous system. Arch. internat. pharmacodynamie. **75:** 222–226.

BERGER, F. M. & W. BRADLEY. 1946. The pharmacological properties of α:β-dihydroxy-γ-(2-methylphenoxy)-propane (Myanesin). Brit. J. Pharmacol. **1:** 265–272.

BERGER, F. M. 1954. The pharmacological properties of 2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate (Miltown), a new interneuronal blocking agent. J. Pharmacol. Exptl. Therap. **112:** 413–423.

BERGER, F. M., M. KLETZKIN, B. J. LUDWIG, S. MARGOLIN & L. S. POWELL. 1959. Unusual muscle relaxant and analgesic properties of N-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate (carisoprodol). J. Pharmacol. Exptl. Therap. **127:** 66–73.

DEL CASTILLO, J. 1948. Central actions of Myanesin. Trab. inst. nacl. cienc. med. Madrid. **12:** 363–385.

FUNDERBURK, W. H. & K. R. UNNA. 1953. Site of action of 2,2-diethyl-1,3-propanediol (Prenderol) on the central nervous system. J. Pharmacol. Exptl. Therap. **107:** 344–355.

FUNDERBURK, W. H., E. E. KING, E. F. DOMINO & K. R. UNNA. 1953. Pharmacological properties of benzazoles. II. Sites of action in the central nervous system. J. Pharmacol. Exptl. Therap. **107:** 356–367.

HENNEMAN, E., A. KAPLAN & K. R. UNNA. 1949. A neuropharmacological study on the effect of Myanesin (Tolserol) on motor systems. J. Pharmacol. Exptl. Therap. **97:** 331–341.

KAADA, B. R. 1950. Site of action of Myanesin (mephenesin, Tolserol) in the central nervous system. J. Neurophysiol. **13:** 89–108.

KING, E. E. & K. R. UNNA. 1954. The action of mephenesin and other interneuron depressants on the brain stem. J. Pharmacol. Exptl. Therap. **111:** 293–301.

MAGOUN, H. W. & R. RHINES. 1946. An inhibitory mechanism in the bulbar reticular formation. J. Neurophysiol. **9:** 165.

MAGOUN, H. W. & R. RHINES. 1947. Spasticity: The Stretch Reflex and Extrapyramidal Systems. Thomas. Springfield, Ill.

SPRAGUE, J. M., L. H. SCHREINER, D. B. LINDSLEY & H. W. MAGOUN. 1948. Reticulospinal influences on stretch reflexes. J. Neurophysiol. **11:** 501–507.

SCHWEITZER, A. & S. WRIGHT. 1937. The action of eserine and related compounds and of acetylcholine on the central nervous system. J. Physiol. **89:** 165–197.

WILKER, A. 1945. Effects of morphine, Nembutal, ether and eserine on two-neuron and multineuron reflexes in the cat. Proc. Soc. Exptl. Biol. Med. **58:** 193–196.

THE EFFECT OF CARISOPRODOL ON THE CENTRAL NERVOUS SYSTEM

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In this paper are reported some results obtained in this laboratory during an investigation on the effect of carisoprodol on the central nervous system. The preliminary results obtained up to the present time concern the influence of the drug: (1) on the cortical and subcortical electric activity, (2) on the motor reaction elicited by electric stimulation of the hypothalamus, and (3) on the electrographic afterdischarge following electric stimulation of the hippocampus.

A total of 8 unanesthetized noncurarized rabbits were used; in addition, 2 animals bearing chronically implanted electrodes on cortical and hypothalamic areas were employed. The techniques of registration and stimulation are described elsewhere (Longo, 1956). A supersaturated aqueous solution of the drug (0.5 per cent) was prepared for each experiment. All injections were made in the ear vein at fixed speed (10 mg./kg./min.).

Action on the Electric Activity of the Brain

FIGURE 1 illustrates the action of increasing doses of carisoprodol on the EEG. The control tracing is in tracing A; between the arrows a vibroacoustic stimulus was applied that evoked an arousal response in all leads. Tracing B was registered 4 min. after the administration of 5 mg./kg. of the drug. Note that the arousal response was partially blocked, and that slow waves appeared on the tracing. At this dose level, muscle weakness was observed in 3 animals, and a short-lasting head drop was noticed in a fourth one. Tracing C was taken 30 min. after tracing B and 5 min. after the administration of carisoprodol (15 mg./kg.). Waves at 4 to 5 cps can be seen in the tracing. The external stimuli are without effect. This dose produced a distinct loss of muscle tone. These effects were of short duration, for after 10 to 15 min. the EEG was normal, and the animal had completely recovered from the paralysis.

With the reservation that only a small number of animals have been used, we have noticed that the drug does not always have the same effect. In fact, 2 animals of 8 treated with the dose of 10 mg./kg. showed, in addition to muscular relaxation, excitatory symptoms such as ataxic gait and searching movements. The EEG in this case showed activation patterns.

FIGURE 2 illustrates the changes of cortical and subcortical EEG after high doses (25 mg./kg.) of carisoprodol. In tracing B slow waves of high voltage are present, together with spikes; electric stimulation of the reticular formation (*horizontal bars*), which in the nontreated animal (*tracing A*) produces activation patterns, remains without effect. After this dose the rabbit is completely paralyzed and has a superficial breathing and a torpid corneal reflex.

Action of Carisoprodol on the Behavioral Changes Produced by the Electric Stimulation of the Hypothalamus

Two rabbits bearing chronically implanted electrodes were used for the study of the influence of carisoprodol on the behavioral changes produced by

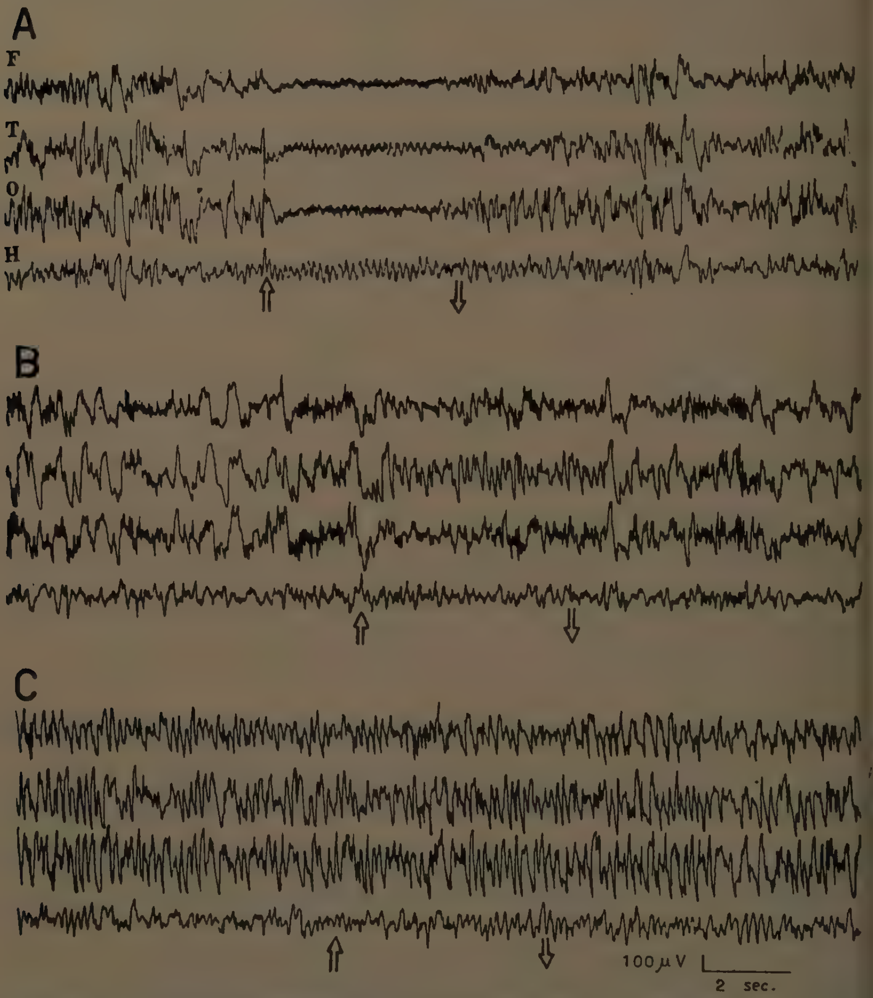

FIGURE 1. The action of carisoprodol on the EEG and on the arousal response to external stimuli in the unanesthetized and uncurarized rabbit. For explanation, see text. Leads: F, frontal; T, temporal; O, occipital; H, dorsal hippocampus.

the electric stimulation of this area. Throughout the experiments the EEG record was taken, and it was possible to observe the concomitant variations of the electric activity of the brain. The sign of behavioral arousal after the stimulation consisted in opening of the eyes and movements of the ears, jaws, and vibrissae. More intense motor effects, such as searching movements and walking, were observed when higher stimulating voltages were used. With doses of carisoprodol between 10 and 15 mg./kg., it was noticed that a slight rise (about 20 per cent of the original voltage) of the threshold for the behavioral response occurred; at the same time a mild paralytic syndrome consisting in ataxia and incoordination of the movements was observed. After such a dose of the drug slow waves may be recorded on the EEG, while the tracing becomes unresponsive to afferent stimuli that would normally produce activation. When the hypothalamus was stimulated with currents of supra-threshold intensity, the movements provoked by the stimulation had perfect coordination, and it seemed that the hypothalamic stimulation produced an

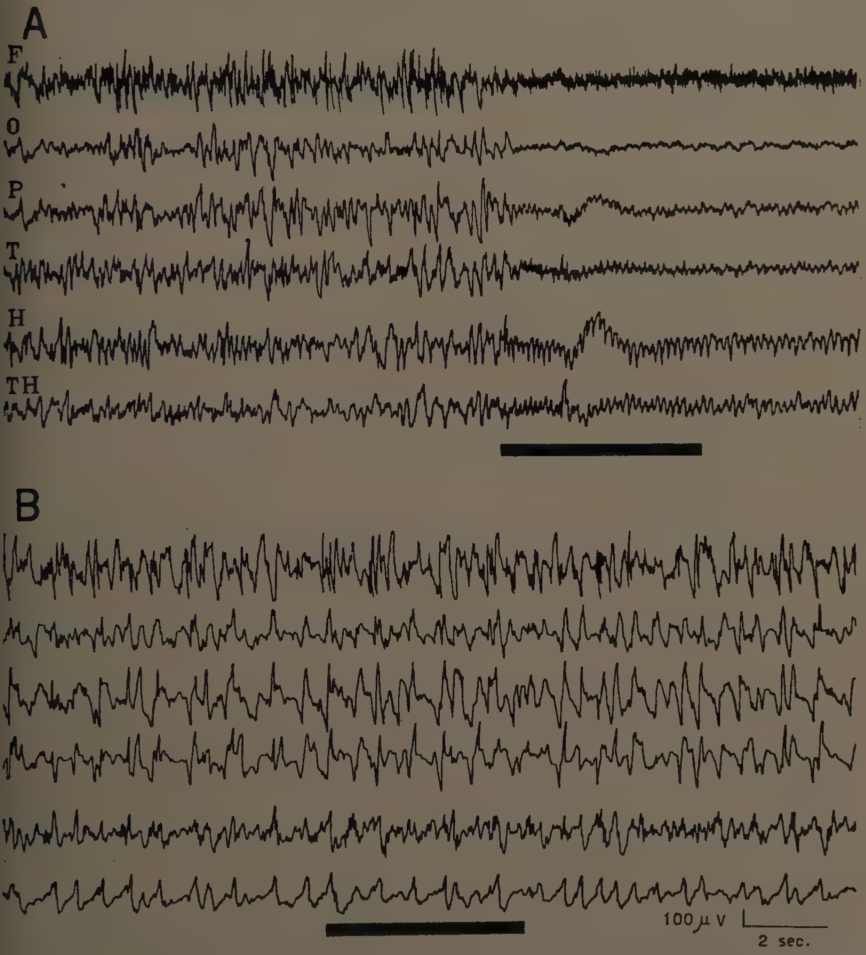

FIGURE 2. The action of carisoprodol on the arousal response obtained with electric stimulation (400 cps, 0.1 msec., 1.3 v) of the reticular formation in the unanesthetized and uncurarized rabbit. For explanation, see text. Leads: F, frontal; O, occipital; P, parietal; T, temporal; H, dorsal hippocampus; TH, anteromedial thalamus.

immediate recovery from muscular weakness. On the other hand, elimination of the slow waves of the EEG paralleled the disappearance of the ataxia. These definite and long-lasting changes of the spontaneous EEG are to be distinguished from the short activation period observed during and immediately after the stimulation. Higher doses (20 to 25 mg./kg.) were followed by complete paralysis, which made the animal lie on its side. Due to this complete paralysis, no further observations of the behavioral response could be made.

The electrographic afterdischarge following the electric stimulation of the hippocampus was not influenced by the administration of carisoprodol up to 10 mg./kg.

Conclusions

Our results confirm the data reported by Berger *et al.* (1959) regarding the action of carisoprodol on the EEG of the curarized cat. The investigations of its effects on the electric activity of the brain have shown a definite influence on brain waves and, in particular, a blocking of the arousal reaction to afferent stimuli and to electric stimulation of the reticular formation, which is not found with other myorelaxants.

From the point of view of its action on the somatomotor system, carisoprodol may be classified as a centrally acting myorelaxant, although some data reported by del Castillo elsewhere in this monograph point out some differences between carisoprodol and the other drugs of this group, such as inhibition of the monosynaptic reflex and a strong influence on decerebrate rigidity. Although it is known (Funderburk *et al.*, 1953; Domino *et al.*, 1952) that in some instances the action of the myorelaxants on the EEG is largely independent of the influence on the somatomotor system, the parallelism between the relaxant action on the rigidity and the blocking of the EEG effects of the stimulation of the reticular substance, which may indicate an action of the drug on sites of the neuraxis more rostral than the spinal cord, must be emphasized.

References

Berger, F. M., M. Kletzkin, B. J. Ludwig, S. Margolin & L. S. Powell. 1959. J. Pharmacol. Exptl. Therap. **127:** 66.

Domino, E. F., K. R. Unna & J. Kerwin. 1952. J. Pharmacol. Exptl. Therap. **105:** 486.

Funderburk, W. H., E. E. King, E. F. Domino & K. R. Unna. 1953. J. Pharmacol. Exptl. Therap. **107:** 356.

Longo, V. G. 1956. J. Pharmacol. Exptl. Therap. **116:** 198.

AN EXPERIMENTAL INVESTIGATION OF THE CHANGE EFFECTED BY THE INGESTION OF CARISOPRODOL, ASPIRIN, CODEINE, AND A PLACEBO UPON THE THRESHOLD FOR DEEP PAIN INDUCED BY ULTRASONIC STIMULATION*

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The analgesic properties of N-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate (carisoprodol) have been described by Berger *et al.*[1] These investigators have indicated that carisoprodol has not shown any analgesic action when evaluated by some of the more commonly used pharmacological tests for analgesia such as the Woolfe and MacDonald[2] hot-plate test, but that it was effective in relieving pain of the type produced by injection of silver nitrate in joints. They suggested that carisoprodol might modify the central perception of certain forms of pain, notably pain and spasm related to skeletal muscles and joints.

Both Hardy *et al.*[3] and Beecher[4] have described comprehensively various methods for the study of pain thresholds. Although Beecher referred to high-frequency sound waves as a means of producing aching pain, he thought the possibility of tissue damage might exclude the technique from use for experimental pain purposes. While there is considerable literature on the use of ultrasonic stimulation as a therapeutic technique, we found no references indicating that the technique had been used previously for evaluating threshold changes related to the ingestion of analgesics.

Ultrasound was chosen as the stimulus against which to test the analgesic ction of carisoprodol, aspirin, codeine, and a placebo because the type of ain produced by high-frequency sound waves emitted from a supersonic scillator has been variously described as deep pain, aching pain, and bone r periosteal pain. Ultrasonic stimulation produces an aching pain that is eep in both the subjective and objective senses: the subject reports the pain o be deep pain, not felt at the surface of the skin; tissue damage, if it results, ccurs in such sites as subcutaneous tissue and muscles, as well as at the kin surface. Pohlman and his associates[5,6] have indicated that damage due o ultrasonic stimulation occurred in areas close to the bone more readily han in homogeneous tissue. They also indicated that periosteal pain always recedes damage and becomes unbearable after a very short time. They easoned that this was due to standing waves that form between the bone nd the sound source. Horvath[7] has shown that a considerable temperature ise occurs between the tissue and bone. This is not to say that much of he ultrasound is not absorbed by the bone. Both Horvath and Schliephake[8,9] ave demonstrated considerable absorption even though the reflection from he bone may be relatively large.

In sum, ultrasonic stimulation produces a deep, aching pain; the concern of this study was both to establish a method and to employ it for evaluating the effects of various analgesics. Carisoprodol, which has been said to alleviate deep pain, was of particular interest. Codeine was included in the group of analgesics evaluated as one means of determing the efficiency of the method, since codeine has been demonstrated by other methods to be an effective agent for raising the threshold for pain.

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Apparatus

Because this study presents a new method for the evaluation of analgesics, the apparatus is described in detail. Various devices for the transmission and application of the ultrasonic stimulus were considered. Pohlman[10] has described the use of water funnels, solid cone-shaped bodies, and the focusing of ultrasound by means of sound lenses and mirrors. The use of a solid cone-shaped body was particularly considered here, and has not yet been abandoned; however, a solid transmitting medium presents complications of its own: it may be subjected to cross-vibration; it may have a critical resonance frequency of its own; and it may absorb a considerable part of the energy it is transmitting. It is probable that the ultrasonic field at the point of emission from a funnel shape, no matter how small the point of emission might be, would not be stable. Therefore, apparatus was used in this experiment that allowed for maximum control of the stimulus. It is desirable to choose a location within the stimulus or ultrasonic field which is known to be of stable and homogeneous intensity. The present arrangement also made possible a very exact measurement of the duration of the stimulation period.

A Dallons U-107 Oscillator-Amplifier with a 12.5 cm.^{2} quartz transducer was used for the ultrasonic stimulation source. The output intensity of this model is continuously variable between 0 and 3.6 w/cm.^{2} The frequency output of this unit is 1000 kcps.

FIGURE 1 is a schematic representation of the apparatus. The metal capsule housing the quartz transducer (*B*) was firmly mounted within the glass basin that is shown schematically. The basin was 24.5 inches long, 16 inches high, and 13 inches wide, and was filled with mineral oil to a level 6 inches below the upper rim. Mineral oil (white, No. 3) was chosen as a transmitting or coupling medium rather than water, since water would have had to be degassed, in order to avoid problems with cavitation. The center of the transducer capsule was 3.5 inches below the surface level of the mineral oil. The transducer was aimed to produce a beam along the center axis of the glass basin. Calibration and/or mapping of the ultrasonic field for the basin used showed that an area along the center line of the beam and 6.75 inches from the front of the transducer capsule was the area of maximum intensity, the intensity distribution across the stimulation area being relatively homogeneous and stable.

The subject's hand was positioned at this point by means of a coordinate calibrating system (*F*), a mirror-crosshair sighting system (*D*, *E*), and a slide support that provided firm positioning of the hands.

To assure that the area to be stimulated on a given subject's hand remained exactly the same from stimulation period to stimulation period, the following alignment procedures were applied. The area of greatest and most homogeneous and stable intensity within the ultrasonic field was found by mapping with thermocouple probes. Then the narrow metal ring shown in FIGURE 1 at the lower end of *F* was brought into position by adjusting the coordinate aligning system horizontally and vertically until the maximum intensity axis of the ultrasonic far field was exactly in the center of the ring (the inner diameter of the ring was 10 mm.). Due to the structure of the far field, this was also an area of homogeneous and stable intensity. The coordinate system to which the ring is attached was then locked. The subject's hand was brought into the desired position by means of the slide support visible in FIGURE 1 behind the extended hand. This support consisted of two rectangular boards, one sliding on and in front of the other. Movement of the sliding board was vertical only; no sidewise movement was possible. The subject's hand was held firmly on the sliding board by means of positioning pegs between the fingers and a nylon strap. The board was slid down along its support board to its terminal position. By means of the mirror-crosshair sighting system (*D*, *E*) it was then possible to adjust the total slide support so that the area to be stimulated, which was marked with ink on the subject's hand, would lie directly behind and barely out of contact with the center of the alignment ring—directly at the point of maximum, stable intensity in the sound field.

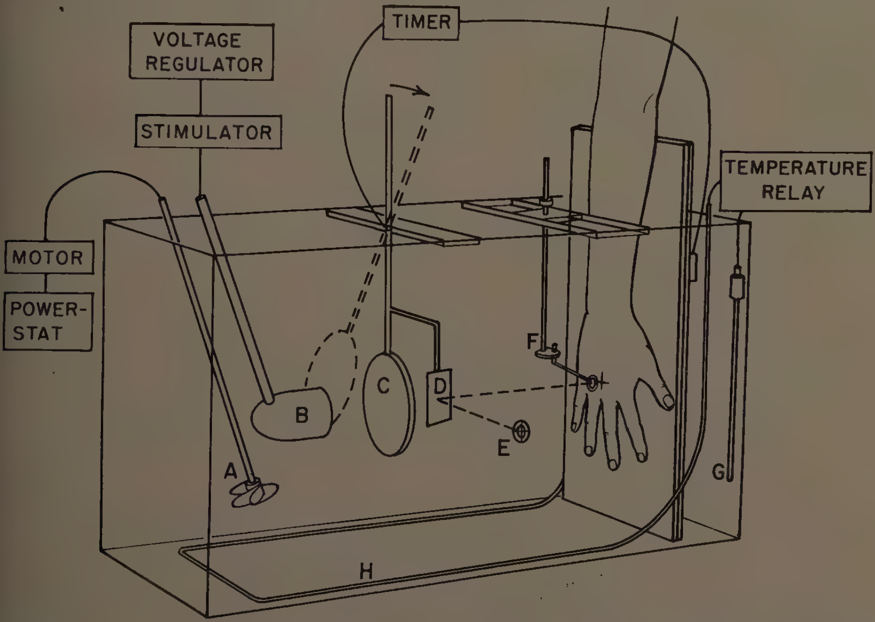

FIGURE 1. Arrangement of apparatus components for experimental stimulation with ultrasound. (*A*) Constant velocity electric stirrer. (*B*) Ultrasonic transducer capsule. (*C*) Mechanical shutter. (*D*) Mirror. (*E*) Cross-hairs. (*F*) Coordinate calibration system with alignment ring. (*G*) Thermostat. (*H*) Heating element.

Thus, with the transducer capsule firmly positioned, the hand firmly positioned, and the coordinate system locked, it was assured that the same intensity of ultrasonic energy was available at the center of the alignment ring for stimulation from trial to trial—provided, that is, that no other variables such as foreign elements in the oil, cavitation, and changes in temperature interfered. The oil was changed frequently and the basin cleaned.

The apparatus was recalibrated several times and the ultrasonic field was remapped. While the approximate data supplied by the Dallons Laboratories denoting the characteristics of the ultrasonic field in the case of their 12.5-cm.[2] transducer may be sufficient for therapeutic applications, the conditions of the present experiment required more exact and extended information. Contrary to the purpose of therapeutic ultrasonic stimulation and instrumentation, the purpose in the present experiment was to produce pain. While the therapeutic application calls for an ultrasonic field that characteristically leads to pain only after very prolonged application with a moving head, the present conditions required a stationary beam and field properties that would lead to periosteal pain of clear and sudden onset in a relatively short period of time. While in most therapeutic applications the radial intensity distribution of the field may not be critical, it was highly critical for this experiment. Under the conditions of this experiment, the stimulation area was very small and exactly defined. It was therefore necessary to find an area in the ultrasonic field where the radial distribution of intensity was homogeneous and stable. Measurement of the ultrasonic field was made with thermocouple probes and a sensitive mirror-galvanometer. A detailed description of this method is given by Pohlman.[10] FIGURE 2 shows the intensity distribution in schematic form. The lens-shaped areas denote relatively homogeneous intensity concentrations within the total ultrasonic field. As may be seen from this illustration, the radial intensity distribution in the proximity of the transducer is markedly irregular, while some distance away there is a single, central, extended intensity lobe. The total field may therefore be divided into a near and a far field, the far field being characteristically more stable and homogeneous. FIGURE 3 shows central intensities at various distances from the transducer, and FIGURE 4 shows radial intensity distributions at distances of 15 cm. and 25 cm. from the transducer. For obvious reasons,

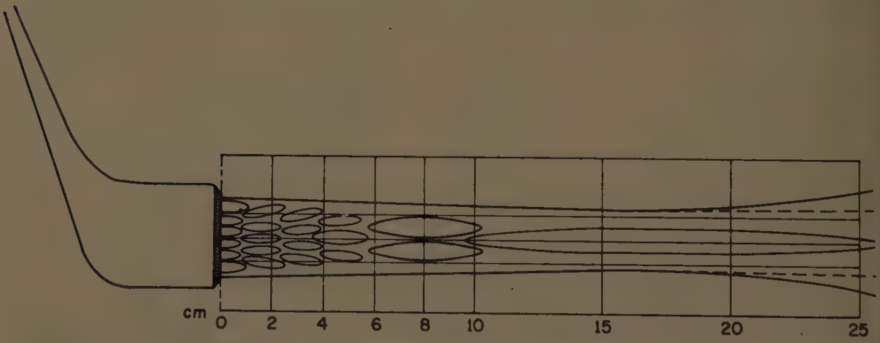

FIGURE 2. Structure of the ultrasonic field. Lens-shaped areas denote relatively homogeneous intensity concentrations.

the point to be stimulated was placed in an area within the far field (the extended central pressure lobe shown in FIGURE 2). By attaching one of the thermocouple probes used for calibration to the alignment ring described above, it was possible to center the ring exactly around the central pressure

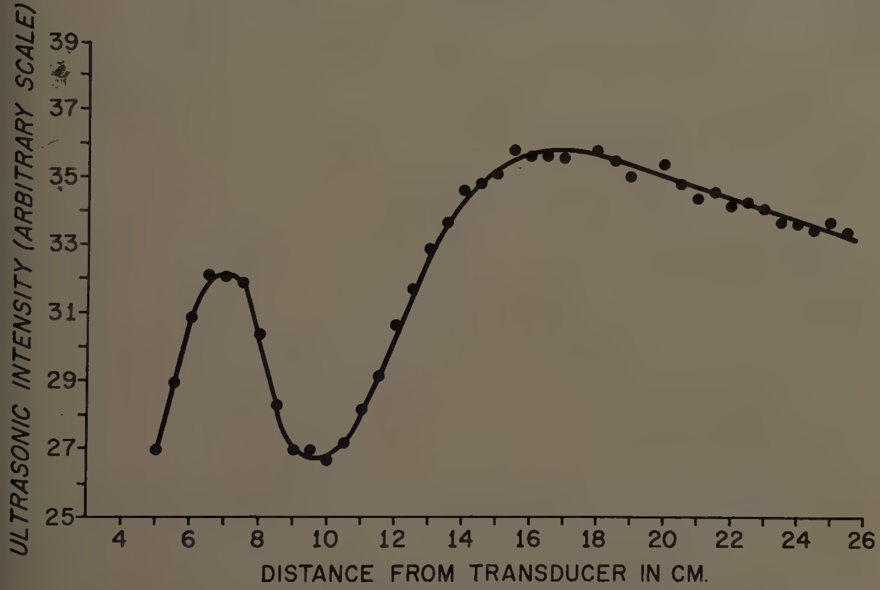

FIGURE 3. Intensity distribution along the central axis of the ultrasonic beam. Reproduced by permission of the *Archives of Physical Medicine and Rehabilitation.*[12]

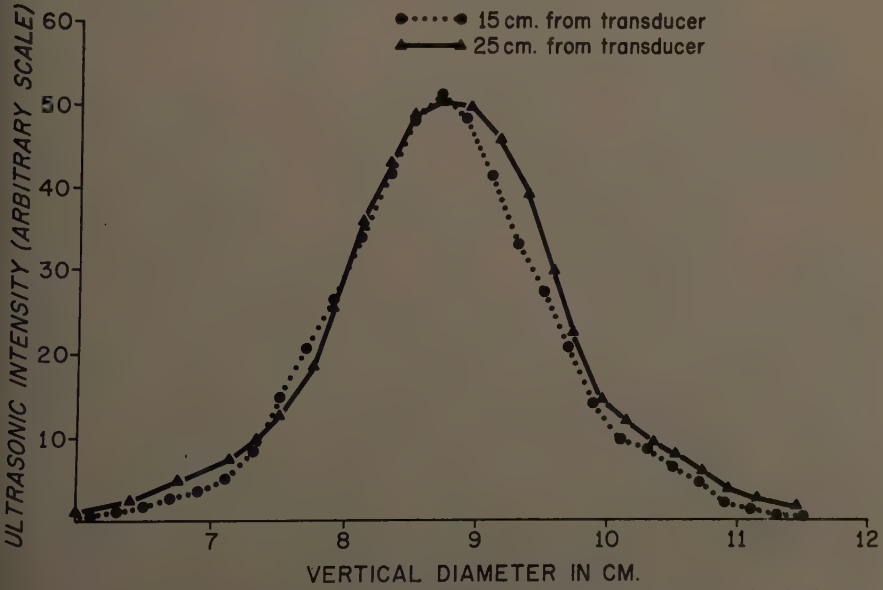

FIGURE 4. Intensity distribution in the vertical diameter of the ultrasonic far field. Reproduced by permission of the *Archives of Physical Medicine and Rehabilitation.*[12]

lobe in the far field. It should be pointed out, however, that the pressure distribution in this central lobe is only relatively homogeneous. As may be seen from FIGURE 4, there is a rather steep gradient on either side of the central intensity point. Even within that part of the stimulation area defined by the metal alignment ring there would be an intensity decrease of from 5 to 10 per cent from center to periphery. It may be seen from the preceding that utmost accuracy was required in calibration as well as in the positioning of the hand. With the instrumental arrangement as described, a positioning accuracy of ±1 mm. was possible. Subjects reported the onset of threshold pain at a point directly at the center of the ring. While frequent recalibration was accomplished, not once did it result in a change in the position of the alignment ring.

The necessity of precise positioning of the subject's hand preceding the experimental period demanded that the ultrasound stimulus be cut off during this time. Furthermore, stimulation conditions required that full experimental sound output be available instantaneously at the beginning of the stimulation period. Since the oscillator-amplifier combination of the Dallons U-107 generator did not allow on-off switching without serious warm-up and transient effects, the beam was controlled and interrupted by a sponge-covered mechanical shutter (*C*, FIGURE 1) mounted between the ultrasound capsule and the hand support.

The timing circuit included an on-off switch correlated with the opening and closing of the shutter; another on-off switch correlated with the upward movement of the sliding support upon the subject's voluntary withdrawal and with a time totalizer calibrated in hundredths of seconds. Opening of the shutter resulted in full-strength stimulation and activation of the timer. Withdrawal of the subject's hand (upward movement of the slide support) opened the timing circuit and meant the termination of stimulation for the subject.

Temperature control of the coupling medium was necessary. Liquids in a stationary state frequently will develop temperature layers or inversion zones; it was thought that an inversion layer might possibly act as a deflector. Since deflection within the ultrasonic field would result in uncontrolled intensity changes, temperature stratification was avoided by stirring the oil at a constant rate (*A*, FIGURE 1). Second, since there is some evidence that periosteal pain may be due to a temperature rise in the periosteum, it would seem important to maintain a constant temperature of the coupling medium, especially in cases where the tissue layers in front of the bone are thin. For these reasons, the temperature of the mineral oil in the present experiment was maintained at a constant 37.5° C.

While the apparatus was constructed with an eye to controlling as many known variables as possible, other problems were encountered that could lead to considerable variation. For example, it was known that air acts as an insulator and deflector where ultrasonic frequencies are concerned. Extreme care was required to avoid the formation of air bubbles in the transmitting medium. However, it did not occur to us early in the study that difficulties would be encountered because of air particles retained on the skin of the subject's hands. The slightest residual air layer between tissue and oil will produce a heat sensation that may develop into a sensation of some magnitude. Pohlman[10] suggests that this heat sensation is due to the deflection of the ultrasound by residual air. It seems to be of paramount importance that the surface of the hand be free of air. This can be accomplished by shaving the area to be stimulated, washing the hands, and by massaging oil into the skin prior to insertion of the hand into the oil bath. If this residual air layer is not abolished, the expected periosteal pain will be preceded and masked by a heat sensation at the surface of the skin. This would result, of course, in considerable variation in the perception of threshold levels of the aching, periosteal pain. Two subjects were lost from the study on this account. As this technique is systematically studied, other sources of error that need to be controlled will, no doubt, be found.

We are attempting currently to devise a pressure-balance form of calibration to replace the thermocouple method because a pressure-balance calibration would make it possible to measure the absolute ultrasonic force at any point within the ultrasonic field at any time.

We also plan to continue to explore the possibility of using a cone containing a solid transmitting medium. If a solid medium could be found that, when formed in a cone shape, would not show maxima and minima in the intensity of the beam at the point of emission, direct contact between the point of emission and the point one wished to stimulate could be made, and the stimulation area could be confined more exactly to the area of contact. Furthermore, one could then use parts of the body other than the hand more conveniently.

Procedure

A constant transducer output of 1.2 w/cm.^{2} amounting to a total of 15 w was used for purposes of stimulation. Some of this energy was lost in transmission, of course; how much is not known. This level of beam intensity was chosen because pilot self-experimentation had indicated that the onset of deep or periosteal pain at this exposure was clear and sudden. Furthermore, the macroscopic and microscopic histologic examination of the skin, subcutaneous tissue, and muscle of guinea pigs that had been subjected to varying intensities and to varying durations of the same intensity indicated that this output was relatively safe up to 20 sec. duration. The ultrasonic stimulus had been beamed to the femora of guinea pigs, each guinea pig being encased in a plastic tube that allowed exposure of the femur; the same apparatus was used for the guinea pigs that were subsequently used for human subjects. In all, 36 guinea pigs were exposed at intensities ranging from 0.8 to 3.6 w/cm.^{2} and for periods of time ranging from 14 to 180 sec. per exposure. The number of exposures ranged from 1 to 9; a guinea pig receiving 9 exposures would have been tested once every half hour over a 4-hour period. TABLE 1 shows the results of the histologic examination for guinea pigs exposed to 1.2 w/cm.^{2} for 20 sec. per exposure. It will be noted that there is some evidence of tissue damage. Damage varied with both intensity and time. The findings were, of course, irregular; that is, one pig might show tissue damage at an intensity evel of 1.7 w/cm.^{2} beamed for a duration of 20 sec.; another pig subjected to he same intensity for the same duration of time might show no damage.

The macroscopic histologic examination for the pigs shown in TABLE 1 indicated the following: pigs No. 4, 11, 12, 19, 27, 25, 34, 23, and 24 showed no gross lesions. Pig No. 28 showed a scattering of tiny subcutaneous petechial hemorrhages; pigs No. 26 and 33 showed a slight edema in the subcutaneous tissue.

In sum, this is not a technique to be used in cavalier fashion. A stationary beam at an angle vertical to the bone can produce damage quite rapidly. Pohlman[10] reports no damage of any sort with ultrasound therapy at an intensity level of 4 w/cm.^{2} administered daily for approximately 10 min. at the same body position. In this case, however, the sound head was in motion.

TABLE 1
MICROSCOPIC EXAMINATION OF GUINEA PIG FEMORA
(20-sec. exposures to 1.2 w/cm.^{2})

Pig No.	No. of exposures	Skin lesions[*]	Subcutaneous tissue lesions[†]	Muscle lesions[‡]
4	1	—	—	+
11	1	—	—	—
12	1	2+	2+	1+
19	1	—	—	—
27	4	—	—	—
28	4	2+	2+	2+
25	5	2+	—	—
26	5	—	+	—
33	5	1+	3+	+
34	5	—	3+	2+
23	9	—	2+	—
24	9	—	2+	—

[*] Skin lesions: 1+, loss of superficial layers of the epidermis involving squamous cell layers only, leaving the basal cell layers intact; 2+, loss of superficial squamous and basal cell layers and mild edema of subcutaneous tissue.

[†] Subcutaneous tissue lesions: 1+, moderate edema; 2+, edema with polymorph leukocytic and lymphocytic infiltration; 3+, more intensive edema and extensive leukocytic infiltration.

[‡] Lesions in the muscle: 1+, interstitial edema; 2+, interstitial edema with leukocytic and lymphocytic infiltration.

The guinea pig data may be somewhat misleading in regard to humans. However, one would wish to err on the side of caution. We engaged in self-experimentation over a 3-month period. Using an intensity output of 1.2 w/cm.^{2}, we frequently exposed ourselves over time intervals as long as 40 sec. The resulting pains noted were transient—no apparent damage ensued. In any case, for purposes of this study, an intensity level of 1.2 w/cm.^{2} was chosen with an arbitrary cut-off point of 20 sec. However, no subject was exposed for the entire 20 sec. under any drug condition, and no subjects reported pain due to exposure during or after the study. The times of exposure ranged from 5.21 to 19.58 sec. We have not explored the technique definitively enough to say whether 1.2 w/cm.^{2} is necessarily the "best" intensity; a lesser output may serve as well. As a matter of fact, the difference between threshold and tolerance levels of pain at the intensity level used is so small that even a lesser intensity might have been better.

Again for reasons of safety, this study was run at threshold rather than tolerance levels.

The point to which the ultrasonic beam was directed was a point on the dorsal aspect of the third metacarpus 1 cm. above the knuckle. A cross was marked in ink at this point to aid in sighting the beam. Both the right and the left hands were used: if a given subject was assigned, at random, to be exposed first on his right hand, his left hand was used the following week. Ideally, one might wish not to use both hands, but it was thought that the subject would receive less total stimulation on a given hand if both hands were used, and therefore damage would be less likely to occur. Pilot work had indicated the possibility that thresholds of the right and left hands might differ. This was not confirmed in the final study, which gave 10.06 as the mean predrug threshold for left-hand exposures, and 10.36 as the mean predrug scores for right-hand exposures. Nevertheless, the procedure of initial randomization was followed to assure that the combination of a given drug tested against a given hand would be arrived at by chance.

Ten subjects were used, ranging in age from 26 to 52 years. These subjects were trained in making threshold judgments of the onset of the aching or periosteal pain before being selected for the study. Fourteen subjects had been selected originally; two were eliminated because of inability to make threshold judgments due to fear of the stimulus, and two were eliminated because of the previously mentioned masking effects due to residual air, which created a barrier between the point to be stimulated and the transmitting medium and resulted in a sensation of surface burning.

The remaining ten subjects were instructed to report once a week at the same hour and on the same day each week. They were instructed to report with empty stomachs. Each subject was tested on 4 days, after being given, each day, one of the following: placebo (corn starch), 60 mg. of codeine, 600 mg. of aspirin, and 700 mg. of carisoprodol. The order in which these were given was random.

The study was double-blind. However, the subjects were not naïve; they were staff members and graduate students in pharmacology. Some subjects commented they thought they had been given a drug rather than a placebo; sometimes they were correct in these comments, and sometimes not.

Each subject was reacquainted with the stimulus on any given test day; this was accomplished by using the hand not to be used for that day's run. He was then given two predrug trials one-half hour apart. The mean of these two trials serves as the predrug score. At the end of the second predrug trial, the subject was given a drug. Postdrug measures were taken at half-hour, one-hour, two-hour, three-hour, and four-hour intervals.

Each subject was instructed at the start of each trial to withdraw his hand at the first, slight sensation of the aching pain he had learned to identify in the training trials, some of which were run at tolerance levels. This was done as an alerting device, for it had been discovered in pilot work that subjects not given drugs tended to become bored and/or fatigued as the experiment progressed, and showed a rise in threshold. Threshold judgments are difficult to make, at best; they require the subject's full attention. Each subject was asked on the day he reported if he had any other pain such as headache; if such pain was present, the trial was postponed until the following day. Other pains have a masking effect and make it more difficult to make threshold judgments.

The subject's hand was positioned, and the instructions were given. When the shutter was moved aside to allow the beam to strike the point on the dorsal aspect of the third metacarpus, it activated a timer. When the subject withdrew his hand, the timer automatically stopped.

Results and Discussion

Each subject's score for each trial represents the amount of time in seconds from the pulling aside of the shutter to allow the full force of the ultrasonic beam to strike, to the time he made his first move toward withdrawal. He had been instructed to withdraw when he first barely perceived the onset of the aching pain. The predrug score is the mean of two predrug scores taken one-half hour apart. TABLE 2 shows the means of the raw scores for each condition. It will be noted that the codeine and carisoprodol groups showed a predrug threshold mean somewhat less than that of the aspirin and placebo groups. An analysis of variance between the predrug scores under the four conditions indicated that this difference between the predrug means did not even approach significance. There was a significant difference between subjects ($p < .01$) which tells us what is already known: that the threshold for pain varies considerably from subject to subject.

TABLE 2
MEAN THRESHOLDS

Drug condition	Predrug threshold (sec.)	Thresholds (sec.) at times (in hours) after drug ingestion				
		½	1	2	3	4
Codeine	9.68	10.65	11.98	11.87	11.96	11.09
Carisoprodol	9.86	10.22	10.87	11.15	10.61	9.97
Aspirin	10.84	10.28	10.19	10.85	10.17	9.75
Placebo	10.49	9.84	9.81	9.60	10.32	9.22

Because of the fact that the threshold for pain varies not only from subject to subject but in the same subject at different times, the raw score means were not used in the statistical analyses for comparisons of groups. The scores entering into the statistical analyses for between-group comparisons are difference scores: the predrug score for each subject on any given test day subtracted from each of his postdrug scores for the condition obtaining that day. FIGURE 5 is a graphic representation of the means of these difference scores for each trial and for each drug condition. Because the predrug score was subtracted from each postdrug score, a rise in a line on the graph represents a rise in the threshold for aching or periosteal pain. It will be noted that the placebo group shows a slight rise in mean threshold at the third postdrug hour. This is an artifact, due entirely to a rise in the threshold scores of two subjects who were unfortunately distracted by a commotion. FIGURE 6 presents the same graphic representation of the data as

FIGURE 5, with the exception that the mean scores for all 4 groups for the third postdrug hour are omitted; FIGURE 6 probably represents more accurately what one would expect to see upon replication of the study; however, one never knows with human subjects.

FIGURES 5 and 6 seem to indicate that, of the four groups, the codeine group showed a faster and higher rise in mean threshold for aching pain, and that this higher mean threshold was maintained over a longer period of time than those for the other drug conditions. Carisoprodol appears to be the next most effective analgesic. Neither aspirin nor a placebo appears to be an effective agent for raising the mean threshold for aching pain.

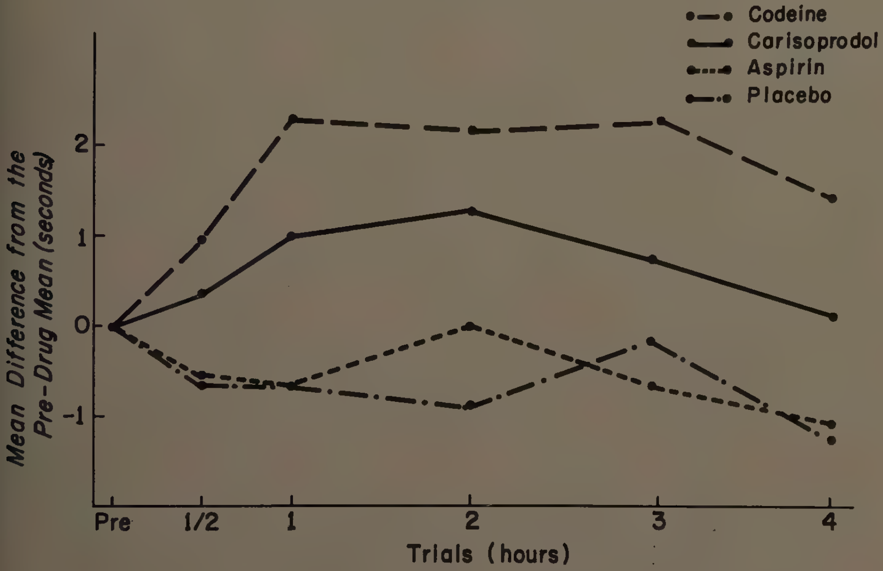

FIGURE 5. Differences between predrug and postdrug means (in sec.) for each of the experimental treatments.

All of the following statistical analyses between groups are based on the data for which the mean differences are shown graphically in FIGURE 5. The statistical analyses across trials for each group are based on the data from which the means shown in TABLE 2 were calculated. It had been predicted that the codeine, carisoprodol, and aspirin groups would show a significantly higher rise in threshold for aching pain than would the placebo group. The correlated *t* comparisons between the means of each of these three groups and the placebo group are one-tailed. The correlated *t* comparisons between the threshold means of the codeine and carisoprodol groups, the codeine and aspirin groups, and the carisoprodol and aspirin groups are two-tailed. It had also been predicted that the codeine, carisoprodol, and aspirin groups would show a significant rise in threshold for aching pain between the predrug and postdrug means. Statistical comparisons across the trials for each of these three groups are one-tailed. The statistical comparisons across trials for the placebo group are two-tailed.

To allow for differences in absorption rates, a mean was derived from the higher threshold score obtained at either the first or second postdrug hour by each subject; this was done for each of the four groups and each mean was compared with the appropriate predrug mean. A mean was also derived from the higher threshold score obtained by each subject at the third or fourth postdrug hour; this was done for each of the four groups, and each of these means was compared with the predrug mean for the same condition.

The codeine group showed a significant rise in threshold for aching pain when the predrug mean and the mean derived from the higher score of the first or second postdrug hour were compared ($p < 0.005$). The carisoprodol group also showed a significant rise in threshold for aching pain when these two means were compared ($p < 0.05$). Neither the aspirin nor the placebo group showed a significant difference between their respective predrug threshold means and the mean obtained for each group by taking the higher score for the first or second postdrug hour. For the comparisons between the predrug mean and the third or fourth postdrug hour mean, the codeine group showed a significant rise in mean threshold for aching pain ($p < 0.01$), as did the carisoprodol group ($p < 0.025$). The aspirin and placebo group showed no significant change in threshold for aching pain when these same comparisons were made.

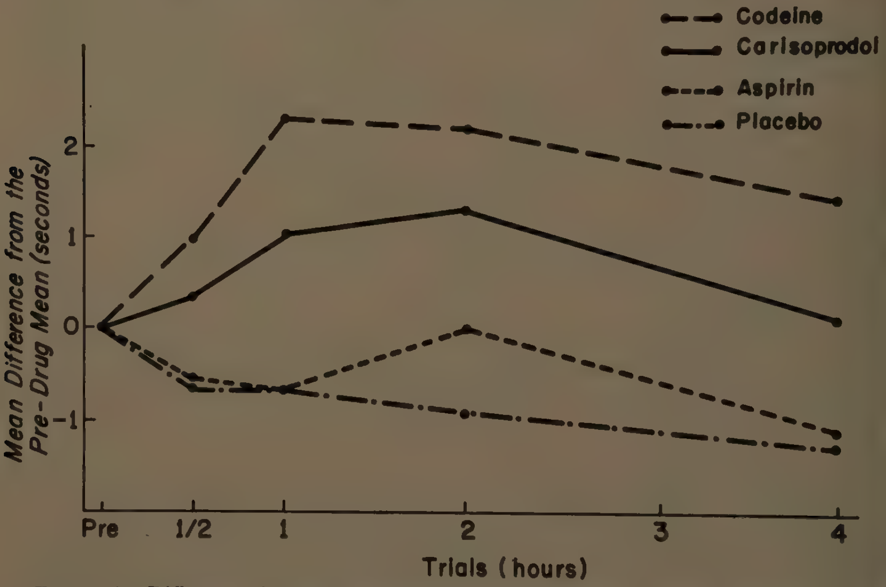

FIGURE 6. Differences between predrug and postdrug means (in sec.) for each of the experimental treatments (third-hour postdrug means omitted).

When comparisons were made across trials without allowing for differences in absorption rates between subjects (each postdrug trial compared with the predrug trial for the same condition), the codeine group still showed a significant rise in threshold for aching pain between the predrug mean and the mean of the measures taken at the first postdrug hour ($p < 0.05$). This group also showed a significant rise in threshold at the second postdrug hour ($p < 0.025$). The aspirin and placebo groups both showed a significant decrease in threshold for aching pain at the fourth postdrug hour; both decreases were significant at the 0.05 level.

For the between-drug comparisons, the difference scores obtained at the first and second postdrug hours were combined to form one mean, as were the difference scores obtained at the third and fourth hours. The threshold means for the codeine groups were significantly higher than those for the placebo group for both the one- and two-hour postdrug comparisons and the three- and four-hour postdrug comparisons ($p < 0.01$). The mean threshold for aching pain of the carisoprodol group was significantly higher than that of the placebo group at the one- and two-hour postdrug comparison ($p < 0.05$). By the time of the third- and fourth-hour postdrug comparison, the carisoprodol group did not differ significantly from the placebo group. No such significant differences were found between the aspirin and placebo groups.

The codeine group showed a significantly higher threshold for aching pain than did the aspirin group for both the one- and two-hour postdrug comparisons and the three- and four-hour postdrug comparisons ($p < 0.05$). The carisoprodol group showed a significantly higher threshold for aching pain than did the aspirin group for the comparison made at the third and fourth postdrug hour ($p < 0.05$). The codeine group did not differ significantly from the carisoprodol group on either comparison.

In sum, the results of this study indicate that both 60 mg. of codeine and 700 mg. of carisoprodol are effective in raising the threshold recognition of deep, aching pain. Furthermore, both this amount of codeine and this amount of carisoprodol effect rises in the deep pain threshold to levels significantly higher than the deep pain threshold for a placebo group. Neither the group which had ingested 600 mg. of aspirin nor the placebo group showed a significant rise across trials in threshold for aching pain, nor did the aspirin group differ significantly from the placebo group. Both these groups showed a significant decrease in threshold for aching pain by the fourth postdrug hour. This decrease may be due to sensitization effects not masked by aspirin or a placebo, but masked by codeine and carisoprodol. In all comparisons, codeine was seen to be a more effective agent in raising the threshold for aching pain than aspirin; the carisoprodol group showed a significantly higher threshold for aching pain than did the aspirin group by the time of the third- and fourth-hour postdrug comparisons.

While no significant differences in threshold for aching pain were obtained between the codeine and carisoprodol groups, an examination of the statistical analyses suggests that codeine in the amount given was consistently the more potent analgesic. One would predict that 60 mg. of codeine would differ significantly from 700 mg. of carisoprodol in the direction of effecting a higher rise in pain threshold, if more subjects were used; however, perhaps not. Studies where dosage is varied need to be done.

It seems fair to say that the method described in this study appears to be one of considerable promise for evaluating analgesics. An examination of the curves shown for the codeine and the placebo groups in FIGURE 5, as well as an examination of the statistical results, certainly indicates that the technique affords a tool of some stability as well as discriminatory power. Using tooth pulp algesimetry, Harris and Blockus[11] have shown that placebos, acetylsalicylic acid, and a mixture of this with phenacetin and codeine all significantly elevate the pain threshold; however, they found no significant differences between the drug conditions. By use of a supersonic stimulus and the method described in this study, it was possible not only to show elevation of the threshold for deep pain under certain of the drug conditions, but also to discriminate between the drug conditions. For example, the codeine group showed not only a significant rise in threshold, but also a significantly higher threshold for deep pain than did the placebo group.

We plan to continue studying the method systematically. For example, intensity levels need to be varied; it may be that a lesser intensity will allow for greater spread between mean scores obtained under drug conditions. It may also be that a lesser intensity might provide a stimulus that would not override the effect of aspirin, as this one did.

Furthermore, while intercorrelations were computed for the placebo group in this study and were certainly promising (three of the thirteen reliability coefficients computed did not differ significantly from zero, while the rest of the *r*'s ranged from 0.65 to 0.87), a definitive reliability study remains to be done, and the reliability of the method for varied intensity levels also needs to be established.

Summary

The use of an ultrasonic stimulus for inducing deep, aching pain is considered in this paper. By use of the method described, it is shown that both carisoprodol (700 mg.) and codeine (60 mg.) resulted in significantly raised thresholds for aching pain. Subjects who had ingested either aspirin (600 mg.) or a placebo did not show a rise in threshold for aching pain. Both the group which had ingested codeine and the group which had ingested carisoprodol are shown to have significantly higher thresholds for aching pain than the group of subjects who had ingested a placebo. The aspirin group did not differ significantly from the placebo group. Both codeine and carisoprodol appeared to be considerably more potent in producing a rise in the threshold for aching pain than either aspirin or a placebo. No significant differences were found between the codeine and carisoprodol groups. However, the data suggest that codeine in the amount given was consistently the more potent analgesic than carisoprodol in the amount given.

Acknowledgments

We are indebted to several of our colleagues at the University of Washington, as follows: to Robert Sharpley, for his construction of the mechanical shutter and timing circuit for the ultrasonic apparatus; to Justus H. Lehmann, of the Department of Physical Medicine and Rehabilitation, University Hospital, University of Washington, for acquainting us with the problems involved in controlling many of the known variables affecting the operation of the ultrasonic apparatus; and to John Thiersch, for his microscopic and macroscopic examination of the samples submitted.

References

1. Berger, F. M., M. Kletzkin, B. J. Ludwig, S. Margolin & L. S. Powell. 1959. Unusual muscle relaxant and analgesic properties of N-isopropyl-2-methyl-2-propyl-1, 3-propanediol dicarbamate (carisoprodol). J. Pharmacol. Exptl. Therap. **127:** 66.
2. Woolfe, G. & A. D. MacDonald. 1944. The evaluation of the analgesic action of pethidine hydrochloride (demerol). J. Pharmacol. Exptl. Therap. **80:** 300.
3. Hardy, J. D., H. G. Wolff & H. Goodell. 1952. Pain Sensations and Reactions. Williams & Wilkins. Baltimore, Md.
4. Beecher, H. K. 1957. The measurement of pain. Pharmacol. Rev. **9:** 59.
5. Pohlman, R. 1939. Über die Absorption des Ultraschalls im menschlichen Gewebe und ihre Abhaengigkeit von der Frequenz. Physik. Z. **40:** 159.
6. Pohlman, R., R. Richter & E. Parow. 1939. Über die Ausbreitung und Absorption von Ultraschall im menschlichen Gewebe und seine therapeutische Wirkung an Ischias und Plexusneuralgie. Deut. med. Wochschr. **65:** 251.
7. Horvath, J. 1947. Experimentelle Untersuchungen über die Verteilung der Ultraschallenergie im menschlichen Gewebe. Aerztl. Forsch. **1:** 357.
8. Schliephake, E. 1935. Schallschwingungen in der Therapie. Klin. Wochschr. **14:** 1689.
9. Schliephake, E. 1949. Ultraschall bei Gelenkerkrankungen. Kongressbericht der Erlanger Ultraschall-Tagung. : 255–257. S. Hirzel. Zurich, Switzerland.
10. Pohlman, R. 1951. Die Ultraschalltherapie. Verlag Hans Huber. Bern, Switzerland.
11. Harris, S. C. & L. F. Blockus. 1952. The reliability and validity of tooth pulp algesimetry. J. Pharmacol. Exptl. Therap. **104:** 135.
12. Lehmann, J. F. & E. W. Johnson. 1958. Some factors influencing the temperature distribution in thighs exposed to ultrasound. Arch. Phys. Med. Rehabilitation. **39:** 347.

ON THE MECHANISM OF CARISOPRODOL ANALGESIA

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Berger *et al.*[1] have shown that carisoprodol does not show any detectable analgesic action when tested by the methods of Woolfe and MacDonald[2] but that, with the silver-nitrate method of LaBelle and Tislow,[3] such action can be detected. The rat treated with silver nitrate recovers the mobility of the joint after treatment with carisoprodol orally even at a dose level incapable of exercising a hypotonic effect. Using two methods, we have evaluated the central analgesic action and the myorelaxant effect of carisoprodol.

Painful Stimulation of the Dental Pulp in the Guinea Pig by Means of an Electric Current

This test has been described by Radouco *et al.*[4] and by Frommel and Fleury.[5] A complete bibliography is to be found in these works. The method consists in placing an active electrode in a perforation of the upper incisor tooth made by a dentist's 0.5-mm. drill. The active electrode is of the dental type, the neutral electrode is lingual. A Grass stimulator with a frequency of 40 cps, square wave, time of stimulation 0.5 sec., is used. The guinea pig registers pain in a characteristic manner by raising its head (FIGURE 1). Batches of 14 animals are used. Individuals that react to a voltage between 2.5 and 3.8 before treatment with the analgesic are used, others being rejected. The pharmacological test is made the day after calibrating each animal, and the rise of voltage necessary to elicit the pain reaction is determined. This procedure gives an indication of the degree of analgesia and is expressed in percentage.

Elsewhere we have reported a source of error using this technique.[6] Pain is manifested by muscular contraction, so that the response to stimulation is, in fact, indirect. Meprobamate acts by the exteriorization of pain,[6] with the result that this drug gives values superior to those of aminopyrine (Pyramidon), using equal dosages. Clinical results confirm this finding. The same error is found in the atropinic test of Straub in the mouse treated with morphine.[7] Here meprobamate, which is not anticholinergic, shows an effect similar to that of solanaceous alkaloids. Thus, the myorelaxant effect of meprobamate interferes with the two techniques and renders their interpretation doubtful.

Fleury's Technique for the Measurement of Muscular Hypotonus

This test is based on the observation that, if a mouse is supported by its tail and is then presented with a wire gauze (0.9 mesh), 5 cm. square, it grips the wire mesh. The maximum weight that the animal can thus support for a minimum of 5 seconds is noted (FIGURE 2). Several batches of 10 to 20 mice each are examined in this way during 3 days before the pharmacological experiments. Each animal has a chart giving its individual reactions in order to determine intra-animal variation. On the fourth day the drug is administered orally at different dose levels, and the animal is tested as before. Each batch serves for only a single test in order to avoid errors due to fatigue. The reduction of weight supported is then calculated in per cent, using the original calibration figures from which graphs of the myorelaxant effect are drawn.

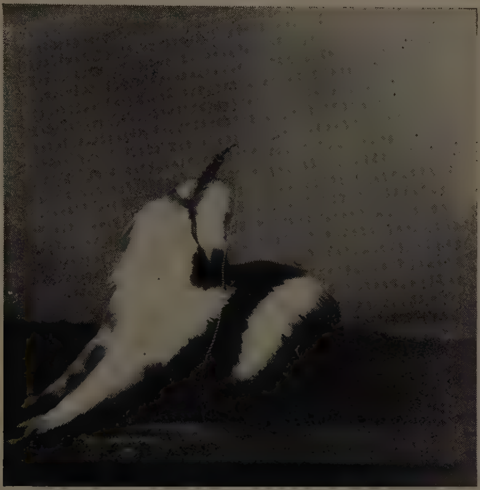

FIGURE 1. Characteristic reaction to pain in the guinea pig.

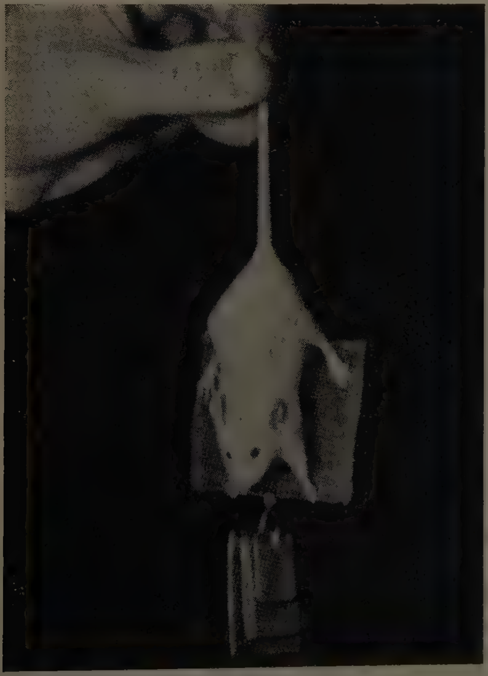

FIGURE 2. Method of determination of the ability of a mouse to sustain weight.

Sensitivity Test Using the Guinea Pig Dental Pulp Method

The analgesic effect of carisoprodol (100 mg./kg., orally), meprobamate (100 mg./kg., orally) and aspirin (100 mg./kg., orally) are expressed in per cent voltage augmentation (threshold stimulation). Controls using phenylbutazone, phenbutadione and aminopyrine are shown in FIGURE 3.

The graphs show that, at equivalent dose levels:

(1) The analgesic effect of carisoprodol reaches +34 per cent. The action lasts for 120 to 150 min.; the maximum is attained at 60 min.

(2) Meprobamate reaches a coefficient of +37 per cent, the maximum being reached at 90 to 150 min., normal sensitivity being regained at 300 min.

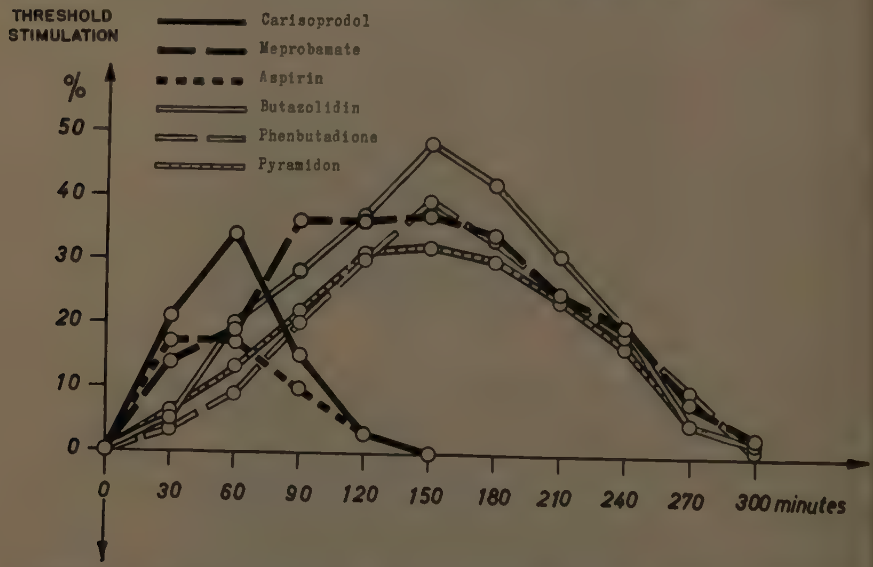

FIGURE 3. Comparative analgesic effects of 100-mg./kg. oral doses of carisoprodol, meprobamate, aspirin, phenylbutazone, phenbutadione, and aminopyrine in the mouse.

(3) Aspirin shows a lower coefficient of +17 per cent, the maximum effect being reached at 60 min., normal sensitivity being regained at 150 min.

(4) The graphs of Phenbutadione and Pyramidon show a moderate action, whereas Butazolidin is more active. The duration of action is about 300 min.

Results Obtained by Muscular Hypotonus Test in the Mouse

FIGURE 4 shows the hypotonic effect of carisoprodol, meprobamate, and aspirin, expressed in per cent. Administration was oral.

The first matter to be noted is that 500-mg./kg. doses of carisoprodol and of meprobamate are subtoxic ones that produce a certain amount of somnolence in the mouse. This state of somnolence falsifies the results given by the Fleury test.[6] This is not the case, however, where the mouse was treated with aspirin (500 mg./kg.). In this case the mouse remained lively and was even hypertonic during the first 30 min. after administration of the drug.

Smaller doses (250 mg./kg.) of carisoprodol and meprobamate are nontoxic and show a hypotonic index of about the same order; only the duration varies. The effect of carisoprodol is of shorter duration than that of meprobamate. Aspirin shows a more inferior hypotonic index than the first 2 medicaments.

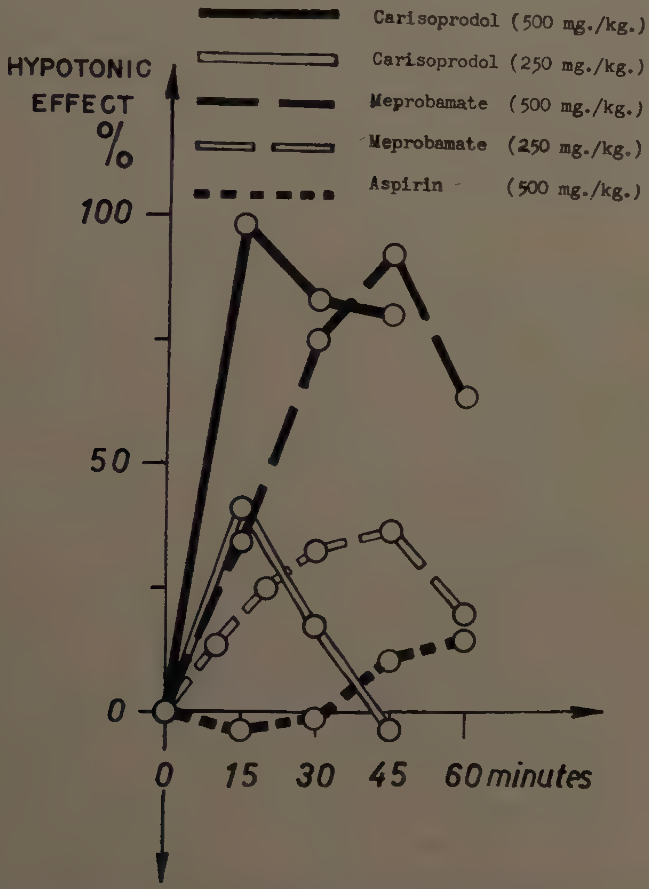

FIGURE 4. Hypotonic effect of oral doses of carisoprodol (500 mg./kg. and 250 mg./kg.). meprobamate (500 mg./kg. and 250 mg./kg.), and aspirin (500 mg./kg.) in the mouse.

Discussion and Conclusion

Our experiments show that a close relationship exists between the effects of carisoprodol, meprobamate, and aspirin. By the dental pulp-stimulation method these drugs show an analgesic effect, and all show a hypotonic effect on striated muscle.

Clinical results have shown, however, that aspirin and carisoprodol are true analgesics, while the action of meprobamate is still under discussion.

The relationship between carisoprodol and aspirin would appear to lie in their antipyretic action. This effect of meprobamate on experimental hyperpyrexia is not significant.

Thus we can conclude from our experiments that carisoprodol is an antithermic analgesic, as is aspirin, and that the former is distinguished from the latter by its greater hypotonic action on muscle. The effect of meprobamate is, on the other hand, centered on its myorelaxant and tranquilizing properties. These pharmacodynamic properties, one being of psychogenic nature and the other peripheral, explain the fact that the patient becomes indifferent to pain on the one hand, and on the other hand is relieved in cases of pain of muscular spasm.

We conclude by remarking that, inasmuch as we have only a proprioceptive method for measuring pain, we have been reduced to interpreting the action of an analgesic as we have done here.

References

1. Berger, F. M., M. Kletzkin, B. J. Ludwig, S. Margolin & L. S. Powell. 1959. Unusual muscle relaxant and analgesic properties of N-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate (carisoprodol). J. Pharmacol. Exptl. Therap. **127:** 66–73.
2. Woolfe, G. & A. D. MacDonald. 1944. The evaluation of the analgesic action of pethidine hydrochloride (Demerol). J. Pharmacol. Exptl. Therap. **80:** 300–307.
3. LaBelle, A. & R. Tislow. 1950. A method of evaluating analgesics of the antiarthralgic type in the laboratory animal. J. Pharmacol. Exptl. Therap. **98:** 19.
4. Radouco, C., S. Radouco & E. Frommel. 1957. Étude quantitative de l'action des analgésiques. Helv. Physiol. Acta. **15:** 193–199.
5. Frommel, E. & C. Fleury. 1958. De la confrontation de quatre méthodes dites d'analgésimetrie. Helv. Physiol. Acta. **16:** 163–170.
6. Frommel, E. & C. Fleury. 1959. Une des causes d'erreur des méthodes d'analgésimetrie en expérimentation animale. Arch. exptl. Pathol. Pharmakol. Naunyn-Schmiedeberg's. **236:** 213–214.

6a. Frommel, E. & C. Fleury. 1958. Tag. Deut. Pharmakol. Ges. : 23–27.

6b. Frommel, E. & C. Fleury. 1958. Helv. Physiol. Acta. **16:** C61–C63.

7. Frommel, E. & C. Fleury. 1959. De l'intérference d'une action papavérinique sur la contraction du muscle lisse à l'acétylcholine et à l'histamine ainsi que sur la tonicité du muscle strié au test de Straub. Compt. rend soc. biol. **153:** 18–20.
8. Fleury, C. 1957. Nouvelle technique pour mesurer l'effort musculaire de la souris, dite test de l'agrippement. Arch. Sci. (Geneva). **10:** 107–112.
9. Frommel, E., P. Gold & C. Fleury. 1957. Méprobamate ou phénobarbital? Schweiz. med. Wochschr. **87:** 1480–1485.
10. Fleury, C. & E. Frommel. 1957. Effet du méprobamate sur le tonus musculaire, mesuré par le test de l'agrippement de la souris. Arch. Sci. (Geneva). **10:** 112–114.

BIOCHEMICAL PHARMACOLOGICAL CONSIDERATIONS OF ZOXAZOLAMINE AND CHLORZOXAZONE METABOLISM

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When the pharmacology of a new drug is studied, an investigation of the metabolism of the drug can yield valuable information. Aspects of drug metabolism that will be presented here include the isolation and identification of metabolites, the pharmacological activity of the metabolites, and the enzymatic mechanisms of drug metabolism. A fourth aspect of studies on the metabolism of drugs that has recently excited our interest is the ability of drugs to accelerate drug metabolism. By this it is meant that the administration of a drug to an animal may actually stimulate the activity of enzyme systems in the animal that metabolize the administered drug or another drug. Such adaptive responses markedly influence the pharmacological activity of the drug. We present here some of our studies with the muscle-relaxant drugs zoxazolamine and chlorzoxazone that furnish an example of a biochemical-pharmacological approach to studies on drug metabolism.

Metabolic Fate of Zoxazolamine and Chlorzoxazone in Man

The metabolism and physiological disposition of zoxazolamine and chlorzoxazone has been investigated in human subjects.[1-3] Following the oral administration of 1.0-gm. doses of zoxazolamine, no detectable drug was found in the urines of these subjects. Evidence was found, however, for the urinary excretion of about 2.0 per cent of the dose as a metabolite in which the amino group of zoxazolamine was replaced by a hydroxyl group (FIGURE 1). This metabolite, identified as chlorzoxazone, possesses muscle-relaxant activity.

Both zoxazolamine and chlorzoxazone are metabolized fairly rapidly in man. Following an oral dose of either drug, peak plasma levels were reached in 3 hours and declined to low values in about 7 hours. Since neither zoxazolamine nor chlorzoxazone was excreted unchanged in the urine, the over-all metabolism of these drugs in man was investigated further. The major route of metabolism of each drug was by hydroxylation at the 6-position of the benzoxazole ring to yield 6-hydroxyzoxazolamine and 6-hydroxychlorzoxazone (FIGURE 1). These phenolic metabolites were excreted chiefly as glucuronides. The free phenolic metabolites were liberated from human urine either by β-glucuronidase or by acid hydrolysis and were identified by comparison with authentic 6-hydroxyl derivatives of zoxazolamine and chlorzoxazone.* The criteria used for the identification of the metabolites included melting points, elemental analyses, chromatographic properties, infrared spectra, ultraviolet spectra, and distribution coefficients. The conversion of zoxazolamine to 6-hydroxyzoxazolamine is a major metabolic pathway in man, since about 60 per cent of an oral dose of zoxazolamine was recovered in the urine as conjugates of 6-hydroxyzoxazolamine. Following an oral dose of chlorzoxazone to human subjects, about 90 per cent of the dose was recovered in the urine as conjugates of 6-hydroxychlorzoxazone.

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* Prepared by J. N. Plampin, McNeil Laboratories, Inc., Philadelphia, Pa.

In our early metabolite isolation studies it was found that urines from zoxazolamine-treated human subjects contained crystals of a substance originally thought to be a hydroxyl metabolite of zoxazolamine. However, upon further investigation, this compound was identified as uric acid. This observation furnished a clue to the potent uricosuric effect of zoxazolamine;[1] the drug has recently been introduced into clinical practice for the treatment of chronic gout.

Our metabolic studies with zoxazolamine and chlorzoxazone in human subjects can be summarized as follows: when zoxazolamine, a compound that possesses both muscle-relaxant and uricosuric properties, is administered to man, a small amount of the dose is recovered in the urine as the active muscle-relaxant drug chlorzoxazone. This compound, however, does not possess uricosuric activity. The major metabolite of zoxazolamine, 6-hydroxyzoxazolamine, lacks both uricosuric and muscle-relaxant activity. The major metabolite of chlorzoxazone, 6-hydroxychlorzoxazone, does not possess muscle-relaxant activity.

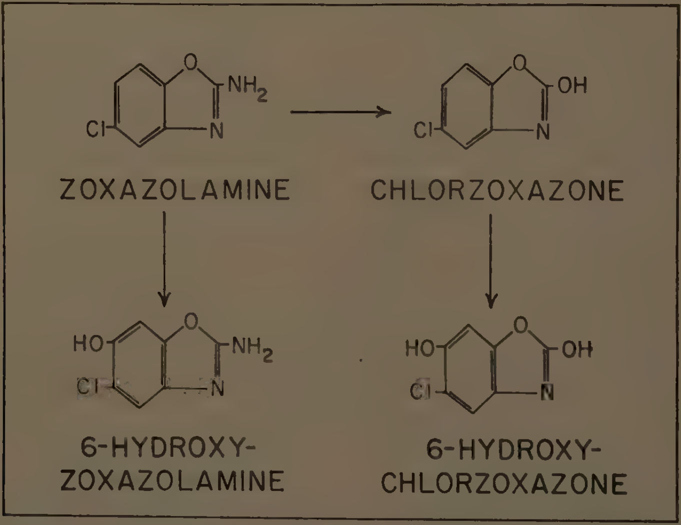

FIGURE 1. Metabolic fate of zoxazolamine and chlorzoxazone in man.

Metabolism of Zoxazolamine and Chlorzoxazone by Rat Liver

Since the results of many studies have shown that various drugs are metabolized by the microsomal fraction of liver,[4] we have investigated the possibility that zoxazolamine and chlorzoxazone were also metabolized by liver microsomes. The various liver fractions were obtained as follows: liver was homogenized in 0.25 *M* sucrose solution and the homogenate centrifuged at 600 g for 10 min. to sediment the nuclear fraction. The resulting supernate, which contained the mitochondria, microsomes, and soluble fractions of the liver cell, was then centrifuged at 8500 g for 15 min. to sediment the mitochondrial fraction. The remaining supernate was then centrifuged in an ultracentrifuge at 100,000 g for 60 min. to sediment the microsomes. The material that was not sedimented is called the soluble fraction of the cell. It was found that the enzyme systems that hydroxylate zoxazolamine and chlorzoxazone to pharmacologically inactive metabolites are localized in the liver microsomes and that these enzymes require reduced triphosphopyridine nucleotide for activity.

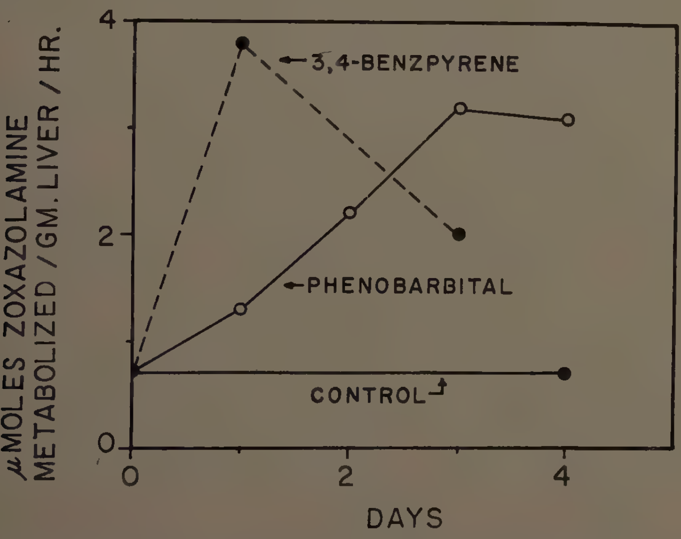

Figure 2. Metabolism of zoxazolamine by livers obtained from rats injected intraperitoneally with either 25 mg./kg. of 3,4-benzpyrene once or with 38 mg./kg. of sodium phenobarbital twice daily.

Adaptive Increases in Drug-Metabolizing Enzymes Induced by Phenobarbital and Other Drugs

In the course of metabolic studies with zoxazolamine an interesting observation was made. It was found that a severalfold increase in the activity of the zoxazolamine-metabolizing enzyme system in the liver was induced by injecting rats* for several days with phenobarbital, barbital, phenylbutazone, aminopyrine, orphenadrine, or 3,4-benzpyrene. The increase in enzyme activity was paralleled *in vivo* by accelerated metabolism of zoxazolamine and by a shortened duration of zoxazolamine paralysis. The effect of pretreating rats with phenobarbital or 3,4-benzpyrene to increase the activity of the zoxazolamine-metabolizing enzyme is shown in figure 2. In this experiment rats were injected intraperitoneally with sodium phenobarbital or 3,4-benzpyrene.

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* The rats used in the experiments given in this paper were all males of the Holtzmann train that weighed 35 to 45 gm. They were kept on a synthetic diet high in all the known vitamins. Results similar to those described in this paper have also been obtained with adult rats.

The animals were sacrificed at intervals, and the livers from control or drug-treated rats were removed, homogenized, and assayed for ability to metabolize zoxazolamine.* The activity of the zoxazolamine-metabolizing enzyme system was doubled after 24 hours and was 300 per cent higher than that of controls after 3 to 5 days of phenobarbital administration. It was found that 3,4-benzpyrene was more potent than phenobarbital; a single injection increased the activity of this enzyme system 400 per cent in 24 hours. The enzyme activity, however, returned toward the control value at later times. Previous studies[5-7] have shown that polycyclic hydrocarbons such as 3,4-benzpyrene and 3-methylcholanthrene stimulate the activity of several drug-metabolizing enzymes in the liver microsomes.

The enzyme in liver microsomes that *N*-demethylates aminoazo dyes (FIGURE 3) has been studied in some detail as an example of a drug-metabolizing enzyme that is stimulated by administration of 3,4-benzpyrene and by several drugs.[5,8,9] This system, which catalyzes the oxidative *N*-demethylation of 3-methyl-4-monomethylaminoazobenzene (3-methyl-MAB) to 3-methyl-4-aminoazobenzene (3-methyl-AB), is localized in the liver microsomes and, like the other drug-metabolizing enzymes, requires reduced triphosphopyridine nucleotide and oxygen for activity. The effectiveness of phenobarbital in stimulating the azo dye-demethylase enzyme system present in the liver microsomes is shown in FIGURE 4. In this experiment rats were injected with sodium phenobarbital and sacrificed 1, 2, 4, and 7 days after drug administration. Livers from control and drug-treated rats were homogenized and assayed for ability to *N*-demethylate 3-methyl-MAB. The activity of this enzyme was tripled in 24 hours and was 5 times higher than that of controls 4 days after the injection of phenobarbital. The activity of the demethylase system returned toward the control value at later times.

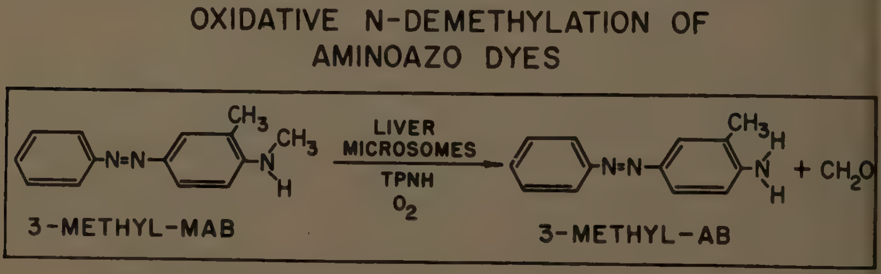

FIGURE 3. *N*-Demethylation of 3-methyl-MAB by liver microsomes.

The available evidence suggests that 3,4-benzpyrene and phenobarbital increase the activity of drug-metabolizing enzymes by inducing their synthesis.[5,6,9] Administration to rats of the amino acid antagonist ethionine completely prevented phenobarbital- or hydrocarbon-induced increases in the activities of several drug-metabolizing enzymes, whereas the simultaneous administration of methionine nullified the inhibitory effect of ethionine on these enzyme systems. Phenobarbital or 3,4-benzpyrene did not increase the activity of the microsomal enzymes when added *in vitro*, and no evidence was found that 3,4-benzpyrene or phenobarbital altered the level of a possible activator or inhibitor in the liver.

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* All enzyme assays described in this paper were carried out in the presence of a system that generated an excess of reduced triphosphopyridine nucleotide.

Studies have been carried out to determine whether pretreatment of rats with drugs that stimulate the zoxazolamine-metabolizing enzyme system would shorten the duration of action of zoxazolamine. Since this drug is hydroxylated to a pharmacologically inactive metabolite, any increase in the activity of the zoxazolamine-metabolizing enzyme system in liver would be expected to shorten the duration of a paralytic dose of zoxazolamine. Indeed, the data given in TABLE 1 show this to be the case. Rats were injected with various drugs for several days, and the animals were sacrificed, their livers were removed, and the ability of the microsomes to metabolize zoxazolamine was determined. Other drug-treated animals were injected with a paralytic dose of zoxazolamine, and the duration of paralysis was measured by determining when the animals regained their righting reflex. It was found that pretreatment of the rats for 4 days with phenylbutazone, aminopyrine, barbital, orphenadrine, phenobarbital, or 3,4-benzpyrene increased the activity of the zoxazolamine-metabolizing system in the liver microsomes and that the increased enzyme activity was correlated with a decreased duration of zoxazolamine paralysis in the intact animals.

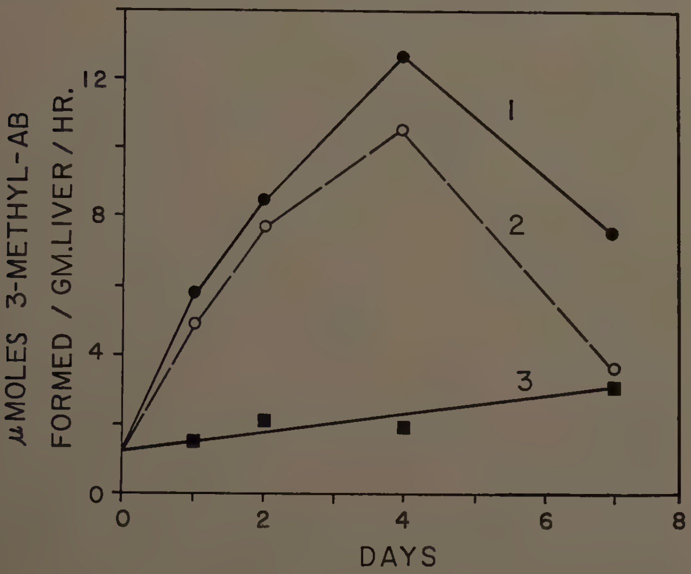

FIGURE 4. *N*-Demethylation of 3-methyl-MAB by livers obtained from phenobarbital-treated rats. Curve 1, rats injected intraperitoneally with 38 mg./kg. of sodium phenobarbital twice daily from day 0 through day 3; curve 2, rats receiving 63 mg./kg. twice daily on day 0 only; curve 3, control animals.

The stimulatory effect of phenobarbital or 3,4-benzpyrene on the rate of zoxazolamine metabolism *in vivo* is shown in FIGURE 5. The greatly accelerated rate of metabolism *in vivo* was also correlated with a shortened duration of action of the drug. The duration of zoxazolamine paralysis in control rats averaged 730 min., in phenobarbital-treated rats 102 min., and in 3,4-benzpyrene-treated rats only 17 min. (TABLE 1).

The possibility was investigated by I. A. Michaelson in our laboratory that pretreatment of rats with various drugs would also shorten the duration of action of meprobamate and carisoprodol[10] (TABLE 2). Pretreatment of rats for 4 days with phenobarbital, barbital, phenylbutazone, orphenadrine, or aminopyrine markedly decreased the duration of a paralytic dose of meprobamate or carisoprodol. Control rats were paralyzed for an average of 1365 min. by meprobamate, while phenobarbital-treated rats were paralyzed for an average of 175 min. Pretreatment of the animals with 3,4-benzpyrene, a compound that shortens the duration of zoxazolamine paralysis (TABLE 1), did not shorten the duration of action of meprobamate or carisoprodol.

TABLE 1

EFFECT OF PRETREATMENT WITH VARIOUS DRUGS ON THE DURATION OF ZOXAZOLAMINE PARALYSIS AND ON THE ZOXAZOLAMINE-METABOLIZING ENZYME SYSTEM IN LIVER MICROSOMES

Pretreatment*	Daily dose (mg./kg.)	Duration of zoxazolamine paralysis (min.)	*In vitro* metabolism of zoxazolamine by liver microsomes (μmoles/gm. liver/hr.)
Control	—	730	0.53
Zoxazolamine	50	555	0.59
Phenylbutazone	125	307	1.05
Benadryl	50	303	—
Aminopyrine	125	263	1.43
Barbital	125	181	1.64
Orphenadrine	50	158	1.64
Phenobarbital	75	102	2.02
3,4-Benzpyrene	25	17	2.63
3-Methylcholanthrene	125	12	—

* Rats were injected intraperitoneally twice daily with drug for 4 days, except for the animals receiving 3,4-benzpyrene or 3-methylcholanthrene, which were injected only once 24 hours before the administration of zoxazolamine. The duration of zoxazolamine paralysis was measured by determining when the rats regained their righting reflex after an intraperitoneal dose of 100 mg./kg. of zoxazolamine. The values given represent averages obtained from at least 5 animals. No enzyme assays were carried out with livers from Benadryl- or 3-methylcholanthrene-treated rats.

The ability of drugs to shorten the duration of hexobarbital hypnosis and to stimulate the liver enzyme system that metabolizes hexobarbital is shown in TABLE 3. It will be noted that pretreatment of rats with 3,4-benzpyrene did not shorten the duration of hexobarbital hypnosis and did not increase the activity of the hexobarbital-metabolizing enzyme system in liver microsomes. Pretreatment of rats with the other drugs, however, markedly increased the activity of the liver microsomes to metabolize hexobarbital, and this increased enzyme activity was correlated with a shortened duration of action of hexobarbital as measured by the sleeping time. Control rats slept for an average of 216 min., while phenobarbital-pretreated rats slept for an average of 11 min.

The ability of phenobarbital to stimulate the activity of liver microsomes to oxidize hexobarbital and to N-demethylate monomethylaminopyrine was studied independently by Remmer in adult rats and rabbits.[11] It is of particular interest that pretreatment of rats with phenobarbital or barbital not only accelerated the rate of hexobarbital metabolism by liver microsomes, but also

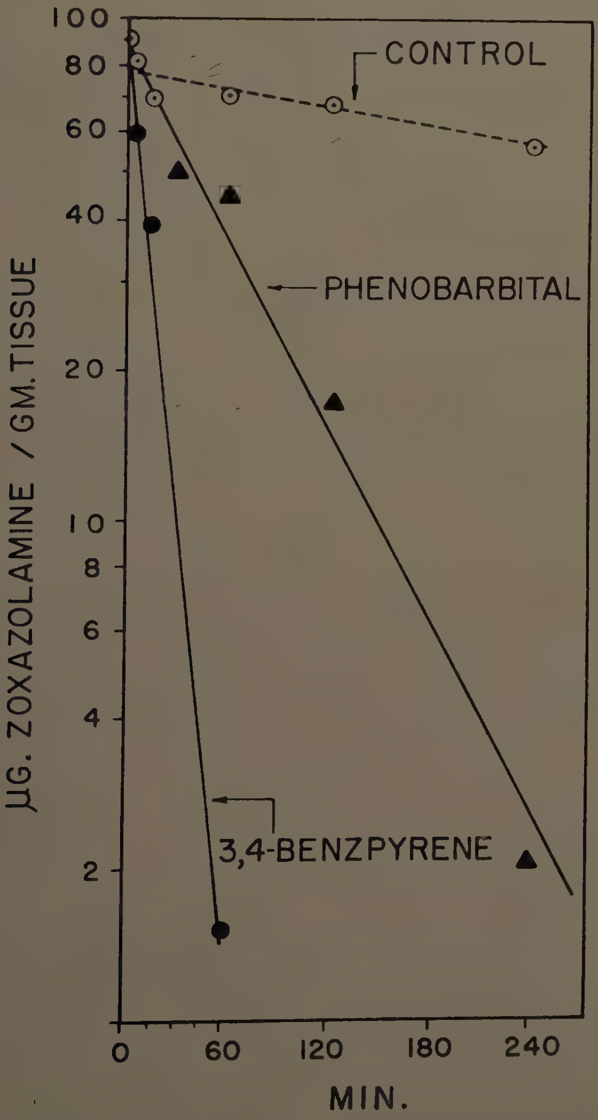

FIGURE 5. Metabolism of zoxazolamine *in vivo* by rats pretreated with 3,4-benzpyrene or phenobarbital. The animals were injected intraperitoneally with either 38 mg./kg. of sodium phenobarbital twice daily for 4 days or once with 25 mg./kg. of 3,4-benzpyrene 24 hours before an intraperitoneal injection of 100 mg./kg. of zoxazolamine. The rats were killed by a blow on the head, skinned, and then homogenized in a Waring blendor. The amount of drug per gram of tissue was determined.

decreased the duration of action of hexobarbital in the intact animals. Our data and those of Remmer suggest that animals may become tolerant to barbiturates because of an accelerated metabolism of the barbiturate to a pharmacologically inactive metabolite.

TABLE 2
EFFECT OF PRETREATMENT WITH VARIOUS DRUGS ON THE DURATION OF MEPROBAMATE AND CARISOPRODOL PARALYSIS

Pretreatment*	Daily dose (mg./kg.)	Duration of paralysis (min.)	
		Meprobamate	Carisoprodol
Control	—	1365	175
3,4-Benzpyrene	25	1347	307
Phenobarbital	75	175	31
Barbital	125	228	55
Phenylbutazone	125	253	72
Orphenadrine	50	293	72
Aminopyrine	125	311	69

* Rats were injected intraperitoneally twice daily with drug for 4 days except that the animals receiving 3,4-benzpyrene were injected only once 24 hours before the administration of meprobamate or carisoprodol. Drug action was considered to persist until the rats regained their righting reflex after the intraperitoneal injection of 250 mg./kg. of meprobamate or 200 mg./kg. of carisoprodol. The values given represent averages obtained from at least 5 animals.

TABLE 3
EFFECT OF PRETREATMENT WITH VARIOUS DRUGS ON THE DURATION OF HEXOBARBITAL HYPNOSIS AND ON THE HEXOBARBITAL-METABOLIZING ENZYME SYSTEM IN LIVER MICROSOMES

Pretreatment*	Daily dose (mg./kg.)	Sleeping time (min.)	*In vitro* metabolism of hexobarbital by liver microsomes (μmoles/gm. liver/hr.)
Control	—	216	0.34
3,4-Benzpyrene	25	302	0.33
Barbital	125	36	1.15
Aminopyrine	125	26	1.02
Orphenadrine	50	23	1.20
Phenylbutazone	125	18	1.24
Phenobarbital	75	11	1.47

* Rats were injected intraperitoneally twice daily with drug for 4 days except that the animals receiving 3,4-benzpyrene were injected only once 24 hours before the administration of hexobarbital. Hexobarbital hypnosis was considered to persist until the rats regained their righting reflex after the intraperitoneal injection of 125 mg./kg. of sodium hexobarbital. The values given represent averages obtained from at least 6 animals.

The effects of various drugs on the activities of several liver microsomal drug-metabolizing enzymes was studied (TABLE 4). Enzyme activities are expressed in relative units per gram of liver, with the control value taken as 1.0. Liver microsomes obtained from rats that were pretreated for 4 days with phenobarbital, barbital, orphenadrine, phenylbutazone, or aminopyrine had an increased ability to metabolize hexobarbital, aminopyrine, phenylbutazone, zoxazolamine, 3-methyl-MAB, and 3,4-benzpyrene. Administration of 3,4-benzpyrene enhanced the metabolism of 3,4-benzpyrene, zoxazolamine, and 3-methyl-MAB, but had no effect on the metabolism of hexobarbital, aminopyrine, or phenylbutazone. It is of particular interest that certain of these drugs stimulated the activity of enzymes required for the metabolism of the same or a closely related drug. Thus, phenobarbital or barbital administration increased the activity of the enzyme system that metabolizes hexobarbital; 3,4-benzpyrene increased the activity of the enzyme system that hydroxylates benzpyrene; phenylbutazone increased the activity of the enzyme system that metabolizes phenylbutazone; and aminopyrine increased the activity of the enzyme system that *N*-demethylates aminopyrine.

In view of the observation that pretreatment of rats with aminopyrine stimulated the liver microsomes to metabolize aminopyrine, an experiment was carried out to determine whether the rate of aminopyrine metabolism *in vivo* was also accelerated. FIGURE 6 shows that rats that were pretreated with aminopyrine metabolized aminopyrine more rapidly *in vivo* than did control rats.

TABLE 4

STIMULATORY EFFECT OF DRUGS ON DRUG-METABOLIZING ENZYMES IN LIVER MICROSOMES

Pretreatment*	Daily dose (mg./kg.)	Enzyme activity†					
		Hexobarbital	Aminopyrine	Phenylbutazone	3-Methyl-MAB	3,4-Benzpyrene	Zoxazolamine
Control	—	1.0	1.0	1.0	1.0	1.0	1.0
Phenobarbital	75	4.3	4.9	9.8	3.6	3.4	3.8
Barbital	125	3.4	4.0	4.3	2.5	2.1	3.1
Orphenadrine	50	3.5	7.3	5.8	5.6	4.3	4.0
3,4-Benzpyrene	25	1.0	0.9	1.4	7.9	19.1	5.0
Phenylbutazone	125	3.7	2.2	10.0	2.4	2.7	2.0
Aminopyrine	125	3.0	2.4	2.4	2.3	3.0	2.7

* Rats were injected intraperitoneally twice daily with drug for 4 days, except for the animals receiving 3,4-benzpyrene, which received injections only once 24 hours before they were sacrificed. The values represent averages obtained from at least 10 animals.

† The enzyme activities are expressed in relative units with the controls taken as 1.0.

It is of interest that those compounds that stimulate the activity of drug-metabolizing enzymes in rats also stimulate ascorbic acid biosynthesis through the glucuronic acid pathway.[8] The finding that the same compounds exert both actions suggests a possible relationship between these two responses. Both effects appear to represent adaptive responses to foreign compounds by a mechanism that does not involve the adrenal gland.[5,11,12]

Summary

Various aspects of zoxazolamine and chlorzoxazone metabolism have been investigated. Both of these drugs are metabolized in man and in the rat chiefly by hydroxylation in the 6-position to yield pharmacologically inactive metabolites. A small amount of zoxazolamine is metabolized in man to chlorzoxazone, a compound that possesses muscle-relaxant activity. During the

course of these metabolic studies it was found that zoxazolamine possesses potent uricosuric properties.

Studies on drug metabolism have led to the finding that pretreatment of rats with a variety of drugs markedly increases the activity of drug-metabolizing enzymes in the liver microsomes. The enhanced enzyme activity is paralleled *in vivo* by an increased rate of drug metabolism and by a shortened duration of drug action. These adaptive responses to drugs have important implications in evaluating the pharmacological activities of drugs that are given repeatedly, either alone or in combination. For instance, pretreatment of rats with phenobarbital shortens the duration of action of zoxazolamine and hexobarbital by accelerating the rate of metabolism of these drugs. Furthermore, pretreatment of rats with phenobarbital also shortens the duration of action of meprobamate and carisoprodol. Pretreatment with certain drugs such as aminopyrine or phenylbutazone can speed up the metabolism of subsequent doses of the same substances. Further investigations are now under way to determine the possible clinical significance of these adaptive responses to drugs.

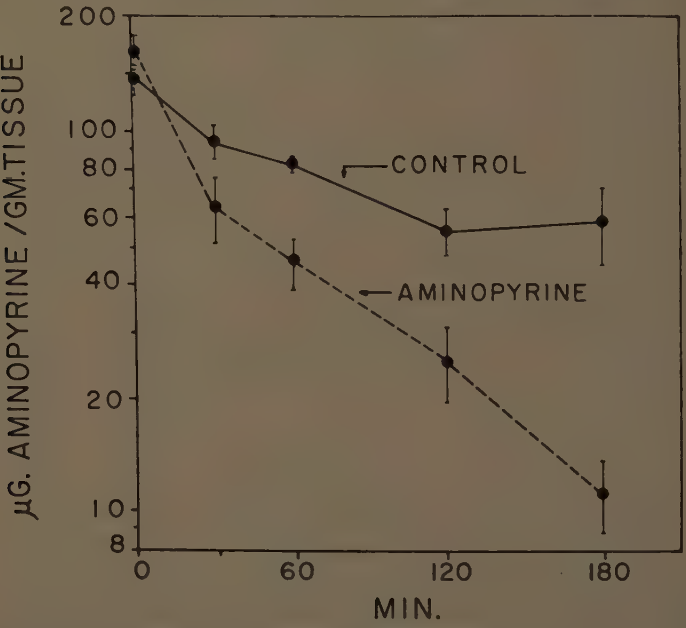

FIGURE 6. The metabolism of aminopyrine *in vivo* by rats pretreated with aminopyrine. The animals were injected intraperitoneally with 63 mg./kg. of aminopyrine in corn oil twice daily for 4 days. On the fifth day the rats were injected with 150 mg./kg. of aminopyrine in saline. The rats were killed by a blow on the head, skinned, and then homogenized in a Waring blendor. The amount of aminopyrine per gram of tissue was determined. Each point is the average value obtained with 5 rats; the vertical lines represent ±1 standard deviation.

References

1. BURNS, J. J., T. F. YÜ, L. BERGER & A. B. GUTMAN. 1958. Zoxazolamine; physiological disposition, uricosuric properties. Am. J. Med. **25:** 401.

2. Conney, A. H., N. Trousof & J. J. Burns. 1960. The metabolic fate of zoxazolamine (Flexin) in man. J. Pharmacol. Exptl. Therap. In press.
3. Conney, A. H. & J. J. Burns. 1960. Physiological disposition and metabolic fate of chlorzoxazone (Paraflex) in man. J. Pharmacol. Exptl. Therap. In press.
4. Brodie, B. B., J. R. Gillette & B. N. LaDu. 1958. Enzymatic metabolism of drugs and other foreign compounds. Ann. Rev. Biochem. **27:** 427.
5. Conney, A. H., E. C. Miller & J. A. Miller. 1956. The metabolism of methylated aminoazo dyes. V. Evidence for induction of enzyme synthesis in the rat by 3-methylcholanthrene. Cancer Research. **16:** 450.
6. Conney, A. H., E. C. Miller & J. A. Miller. 1957. Substrate-induced synthesis and other properties of benzpyrene hydroxylase in rat liver. J. Biol. Chem. **228:** 753.
7. Conney, A. H., J. R. Gillette, J. K. Inscoe, E. R. Trams & H. S. Posner. 1959. Induced synthesis of liver microsomal enzymes which metabolize foreign compounds. Science. **130:** 1478.
8. Conney, A. H. & J. J. Burns. 1959. Stimulatory effect of foreign compounds on ascorbic acid biosynthesis and on drug-metabolizing enzymes. Nature. **184:** 363.
9. Conney, A. H., C. Davison, R. Gastel & J. J. Burns. 1960. Adaptive increases in drug-metabolizing enzymes induced by phenobarbital and other drugs. J. Pharmacol. Exptl. Therap. In press.
10. Conney, A. H., I. A. Michaelson & J. J. Burns. 1960. Accelerated drug metabolism in rats pretreated with drugs. Federation Proc. In press.
11. Remmer, H. 1959. Der beschleunigte Abbau von Pharmaka in den Lebermikrosomen unter dem Einflusz von Luminal. Arch. exptl. Pathol. Pharmakol. Naunyn-Schmiedeberg's. **235:** 279.
12. Burns, J. J., C. Evans & N. Trousof. 1957. Stimulatory effect of barbital on urinary excretion of L-ascorbic acid and non-conjugated D-glucuronic acid. J. Biol. Chem. **227:** 785.

COMPARATIVE EFFECTS OF CERTAIN NONNARCOTIC CENTRAL NERVOUS SYSTEM ANALGESICS AND MUSCLE RELAXANTS ON THE PITUITARY ADRENOCORTICAL SYSTEM*

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Introduction

This monograph is concerned primarily with the pharmacology of analgesic agents with regard to their modification of pain perception at various levels in the central nervous system. Pain is also of interest to adrenal physiologists such as ourselves, since it constitutes a most potent activator of the pituitary adrenal system. Drugs that act upon the central nervous system to suppress pain would be expected also to affect those adrenal cortical responses that are physiological concomitants of painful stimuli, such as the rise in cortisol secretion. Thus it seemed of interest to investigate the influence of various psychotropic agents upon adrenal cortical activation.

Certain areas of the brain, notably the hypothalamus,[1-3] critically influence the regulation and release of corticotropin by the hypophysis. Several well-known pharmacological suppressants of cerebral function such as morphine,[4] barbiturates,[5] and diphenylhydantoin[6] have been reported to impair pituitary ACTH secretion, probably through inhibition of hypothalamic centers.[2] Animal studies indicate that chlorpromazine[7] and reserpine[8] also suppress corticotropin release through hypothalamic inhibition. In man, chlorpromazine has been found to prevent the increase in plasma 17-hydroxycorticoids induced by insulin hypoglycemia.[9] However, the noxious nature of the stimuli necessary to evoke corticotropin release has somewhat limited investigations regarding the influence of analgesic and ataractic drugs upon pituitary-adrenal-cortical function in human subjects.

A quantitative as well as more convenient approach to this problem was suggested by recent work on a relatively nontoxic analogue of amphenone, SU-4885.[10] This agent acts within the adrenal cortex to inhibit enzymatic hydroxylation of carbon 11 in the cortisol molecule, thereby reducing synthesis of biologically active cortisol.[11,12] The decline in circulating cortisol that follows provides a nontraumatic stimulus to corticotropin secretion by the pituitary (FIGURE 1). The increase in urinary 17-ketogenic steroids (17-KGS) that the adrenal is stimulated to secrete under these conditions, particularly 11-desoxycortisol and related compounds, can then be measured. Thus the rise in 17-KGS excretion above basal levels noted after administration of SU-4885 reflects secretion of endogenous ACTH.

In the preliminary studies presented here, a standardized test procedure with SU-4885 has been employed to evaluate the effect of various drugs known to affect the central nervous system upon pituitary and adrenal function.

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Materials

Preliminary studies on 20 patients given therapeutic amounts of 5 pharmacologically different drugs are reported. Within the phenothiazine series, principally chlorpromazine (100 to 200 mg. daily) was used; single studies were made with certain of its congeners such as perphenazine (24 mg. daily), fluphenazine (1.0 mg. daily), and dibenzazepine* (150 mg. daily). The other agents given were carisoprodol† (2100 mg. daily), nialamide (100 to 150 mg. daily), meprobamate‡ (1600 to 2400 mg. daily), and reserpine§ (1.0 to 2.0 mg. daily). The drugs were administered orally in divided doses, usually at 6-hour

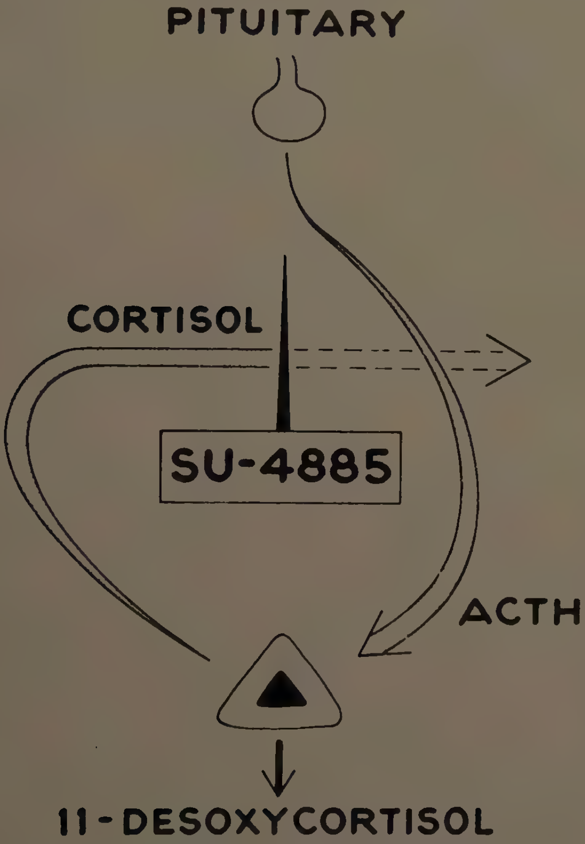

FIGURE 1. Mechanism of action of SU-4885. Removal of cortisol by SU-4885 inhibition of adrenal cortex leads to increased pituitary corticotropin secretion.

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* Supplied as Tofranil through the courtesy of B. W. Rockliff of Geigy Pharmaceuticals, New York, N.Y.

† Provided through the courtesy of J. R. Mote as Soma, produced by Wallace Laboratories, New Brunswick, N.J.

‡ Provided through the courtesy of J. R. Mote as Miltown, produced by Wallace Laboratories.

§ Supplied as Serpasil through the courtesy of C. H. Sullivan, Ciba Pharmaceuticals, Inc., Summit, N.J.

intervals for a minimum of 3 days, the average length of treatment being 1 week except in the case of reserpine, which was usually given for an average of 3 weeks.

Prior to drug treatment, tests with SU-4885 were made as follows: urine specimens were collected during 12-hour periods for 3 days; the first day's collection was used to estimate basal 17-KGS output, as well as the diurnal pattern of urinary 17-KGS excretion; SU-4885 ditartrate* (30 mg./kg.) in 1000 ml. of 0.9 per cent saline was given as a 4-hour intravenous infusion on the second day. On the third day the same infusion was repeated, with the addition of 25 U.S.P. units of corticotropin† to the infusion. In normal individuals the basal 24-hour output of 17-KGS is doubled following the administration of SU-4885 ditartrate in the manner described.[10] The studies were repeated during the treatment period.

Methods

Urine specimens were assayed for 17-KGS by a modification[13] of the Norymberski procedure.[14] To minimize the possibility that drugs might interfere with methodology, responses to SU-4885 were compared to basal values. The effect of these agents, if any, was thus reflected equally throughout all studies, influencing basal 17-KGS output as well as the response to SU-4885.

Results

Mechanism of action of SU-4885. The ability to increase basal 17-KGS excretion following administration of SU-4885 is dependent upon normal hypothalamic and pituitary function. Individual studies in one patient with hypothalamic narcolepsy and another with a chromophobe adenoma of the pituitary illustrate the marked diminution in response, as compared to normal, in the presence of these disorders (FIGURE 2). The humoral interrelationships between anatomic sites involved in producing a positive response to SU-4885, that is, an increase above basal 17-KGS excretion, are schematically diagrammed in FIGURE 2. Note that disorders of the hypothalamus, pituitary or adrenal cortex, thyroid, and liver may decrease response to the cortisol (F) deficit induced by SU-4885.

The decline in plasma cortisol, which provides the stimulus to corticotropin release, results primarily from the interference in corticoid biosynthesis induced within the adrenal cortex by SU-4885. The compound itself does not appear to hasten the clearance of cortisol from plasma (FIGURE 3), nor does it enhance the removal of the biologically essential 20-21 carbon chain from the cortisol molecule (FIGURE 4).

SU-4885 does not influence procedures commonly used for estimating cortisol or 11-desoxycortisol (FIGURE 4). As demonstrated by the same study, significantly larger quantities of the urinary metabolites of both corticoids are estimated as 17-KGS rather than as Porter-Silber chromogens (FIGURE 4).

Effect of changes in adrenal mass and pituitary function upon the SU-4885

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* 1,2-bis-(3-pyridyl)-2-methyl-1-propanone (SU-4885), supplied by C. H. Sullivan, Ciba Pharmaceuticals, Inc.

† Injection of corticotropin provided by H. C. Peltier, The Upjohn Company, Kalamazoo, Mich.

response. Comparison of response to SU-4885 before and after unilateral adrenalectomy indicates that, while the absolute 17-KGS rise diminishes following surgery, the capacity of the pituitary to double 17-KGS output following SU-4885 remains essentially unchanged. The ability of the remaining adrenal to respond to exogenous ACTH was also unaffected, inasmuch as the observed 17-KGS rise continued to be proportional to basal levels.

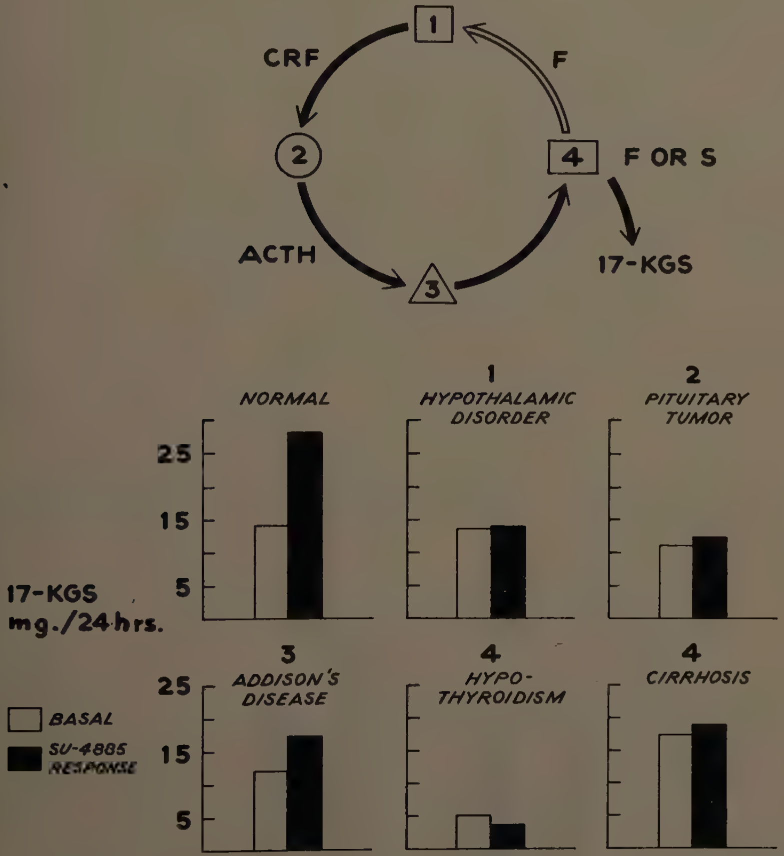

FIGURE 2. Localization of block to SU-4885 response. Note the absence of response with lesions in sites (1) and (2), the small but definite response with partial adrenal insufficiency (3) but normal pituitary function. In both hypothyroidism and cirrhosis the response is presumably impaired because of delayed clearance of cortisol by the liver (4). Key: CRF, corticotropin releasing factor; F, cortisol; S, 11-desoxycortisol.

The effects of pituitary irradiation were in marked contrast to those of unilateral adrenalectomy (FIGURE 5). Although in both situations basal 17-KGS production was not significantly altered by therapy, pituitary irradiation sharply reduced the proportional increase in 17-KGS output relative to basal levels when SU-4885 was given alone or with added exogenous ACTH.

Effect of psychotropic agents on basal output of urinary 17-KGS. The drugs studied produced no striking effects upon basal urinary 17-KGS excretion

(FIGURE 6). A moderate increase of 4 to 5 mg./day was noted with the phenothiazine compounds, as well as with carisoprodol, whereas reserpine caused a decrease of approximately 5 mg./day in basal levels. The normal diurnal pattern of 17-KGS excretion was retained during the treatment period although, in the 3 cases given carisoprodol, a tendency toward a flattening of the diurnal fluctuation was observed.

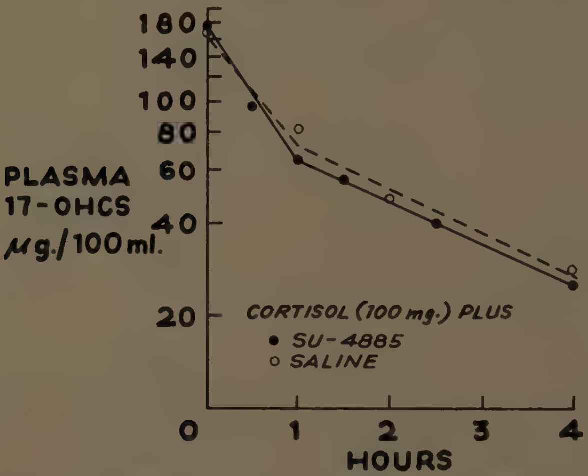

FIGURE 3. Effect of SU-4885 on plasma clearance of cortisol. Note absence of any effect of SU-4885 ditartrate (30 mg./kg. body weight) upon plasma clearance of cortisol in a totally adrenalectomized patient.

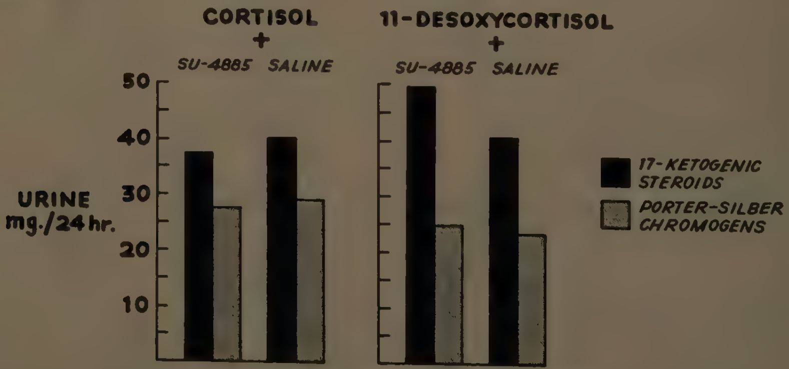

FIGURE 4. Influence of SU-4885 upon metabolism and measurement of corticoids. Note the essentially similar urinary recoveries of cortisol and 11-desoxycortisol respectively as 17-ketogenic steroids and Porter-Silber chromogens in the presence or absence of SU-4885 in a totally adrenalectomized patient.

Effect of psychotropic agents on the response to SU-4885. A significantly decreased response to SU-4885 (amounting to approximately 50 per cent of pretreatment rises) was observed in each case studied during treatment with phenothiazines, carisoprodol, and nialamid (FIGURE 7). The similar action of these 3 compounds was in contrast to the findings with reserpine, where the rise above control levels following SU-4885 administration remained unchanged.

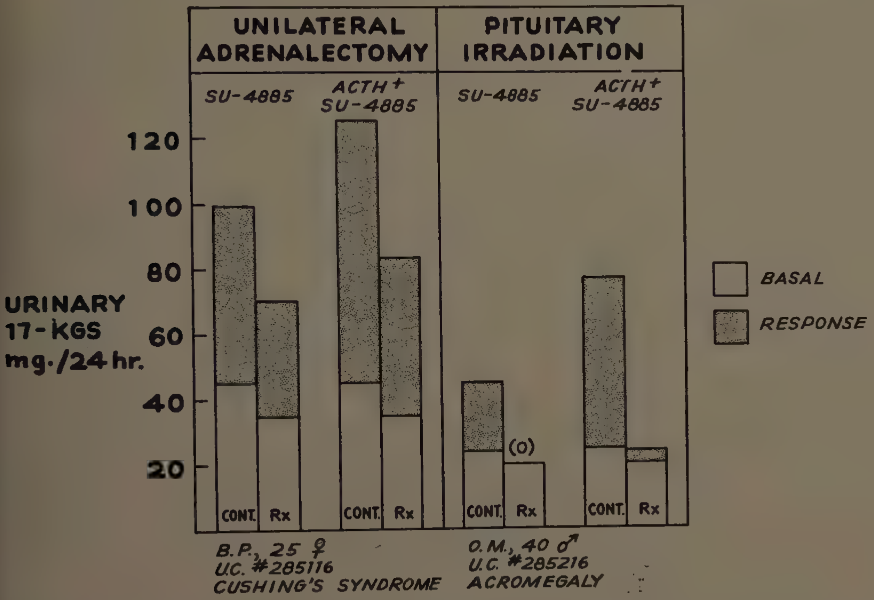

FIGURE 5. The effect of changes in adrenal or pituitary function upon the response to SU-4885. Note that response remains unchanged after unilateral adrenalectomy, whereas there is a marked reduction after pituitary irradiation.

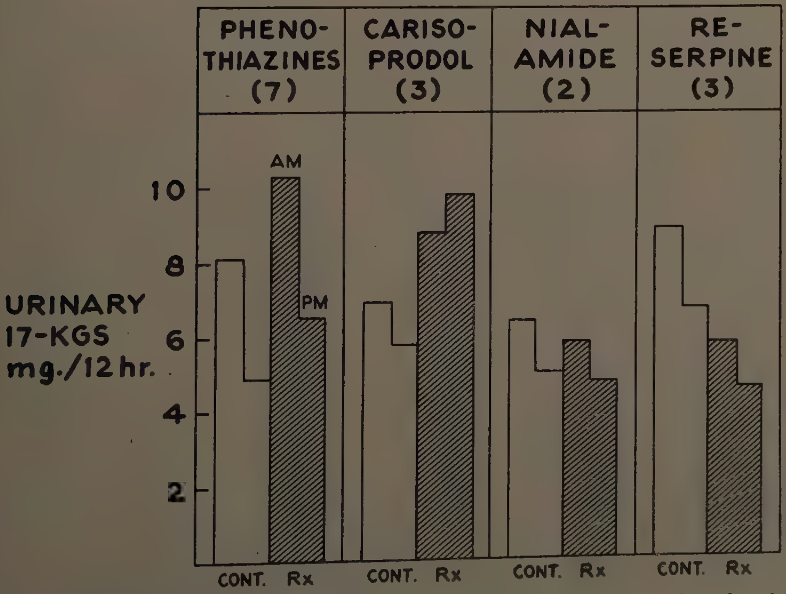

FIGURE 6. Effect of psychotropic agents upon basal 17-KGS excretion and diurnal variation.

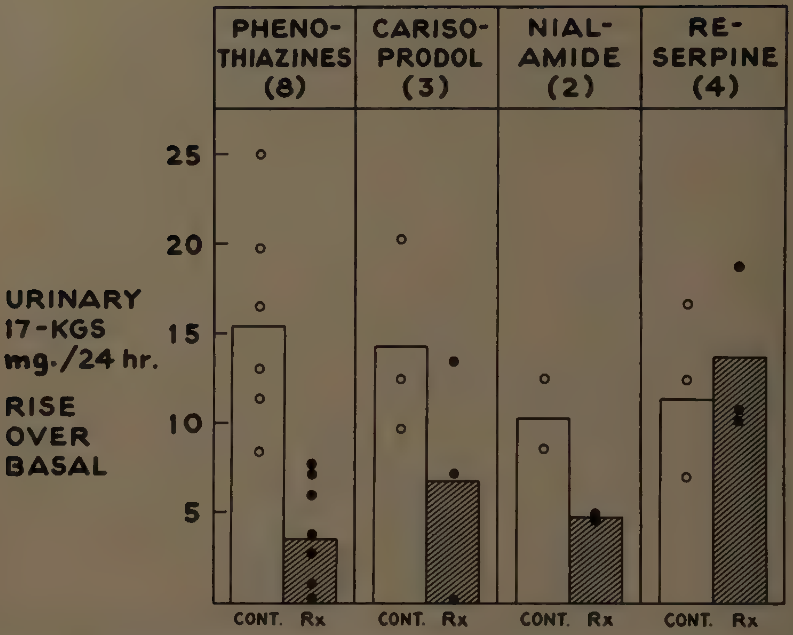

Figure 7. Modification of pituitary response to SU-4885 by psychotropic agents. Each point represents the value for an individual experiment.

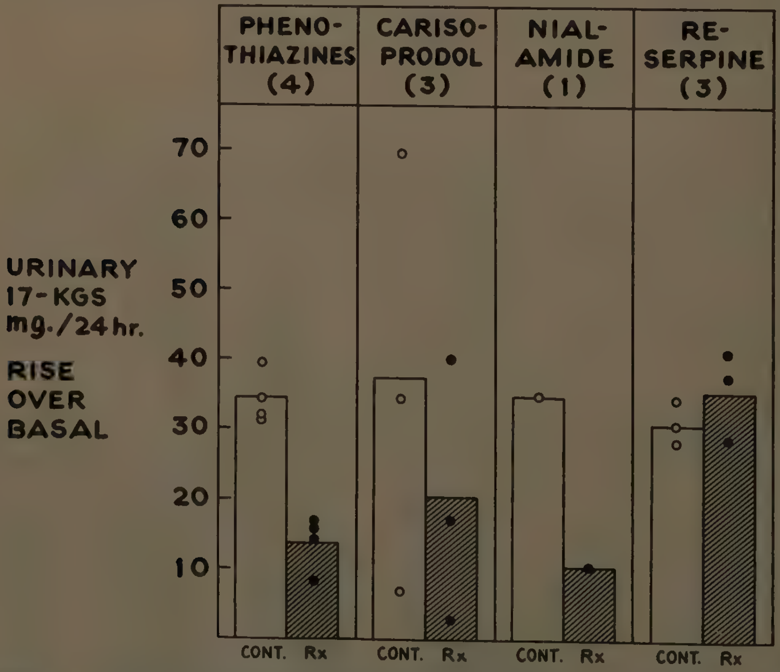

Figure 8. Modification of adrenocortical response to ACTH + SU-4885 by psychotropic agents. Each point represents the value for an individual experiment.

Effect of psychotropic agents on adrenocortical response to exogenous ACTH. Each of the agents found to impair responsiveness to SU-4885 (FIGURE 7) also led to a decline of approximately 50 per cent in the level of 17-KGS attained when SU-4885 was given together with 25 U.S.P. units of corticotropin (FIGURE 8). Reserpine had no effect upon the response of the adrenal cortices to exogenous ACTH.

Suppression of pituitary-adrenal responsiveness with carisoprodol and meprobamate. In view of the close structural similarity of meprobamate to its isopropyl derivative carisoprodol, the pituitary-adrenal effects of these compounds were compared in 2 subjects given both drugs on separate occasions (TABLE 1). A marked suppression of the ability to increase basal 17-KGS levels in response to SU-4885 given alone or with added ACTH was found with both agents.

Effect of chlorpromazine in patients with low ACTH reserve. Three patients found to have an impairment in pituitary corticotropin release as revealed by SU-4885 tests (presumably resulting from a pituitary tumor, previous pituitary irradiation, or corticoid therapy) were given chlorpromazine and retested during therapy (FIGURE 9).

TABLE 1

SUPPRESSION OF PITUITARY ADRENAL RESPONSIVENESS BY STRUCTURALLY SIMILAR BUT PHARMACOLOGICALLY DIFFERENT COMPOUNDS

Subject	Control*			Carisoprodol			Meprobamate		
	Basal	Increase†		Basal	Increase		Basal	Increase	
		SU-4885	SU-4885 + ACTH		SU-4885	SU-4885 + ACTH		SU-4885	SU-4885 + ACTH
E. W.	14.1	12.2	34.6	11.7	7.1	17.3	13.2	6.1	22.2
G. B.	12.8	10.2	31.6	15.0	6.5	2.6	16.4	1.2	−1.9

* All data expressed as milligrams of urinary 17-ketogenic steroids per day.
† Indicates rise above basal level during each period.

These patients, whose basal 17-KGS excretion was normal, continued to be unresponsive to SU-4885 during drug therapy and, in addition, showed no diminution in adrenocortical sensitivity to exogenous ACTH. The latter finding is in marked contrast to the reduction in adrenocortical response to administered ACTH that occurred when patients with normal pituitary function were given chlorpromazine.

Discussion

Certain drugs noted primarily for their analgesic or psychotropic properties were investigated with regard to their effects upon basal adrenocortical function, as well as upon the intrinsic mechanisms whereby the pituitary increases adrenocortical activity above resting levels. The bulk of the study was carried out with chlorpromazine, since earlier work by Christy *et al.*[9] suggested that this agent impaired the release of pituitary corticotropin that normally occurs with insulin hypoglycemia.

The basal output of urinary 17-KGS, representing the total 24-hour adrenocortical activity, was not affected significantly by pretreatment with chlorpromazine, carisoprodol, meprobamate, or nialamide. Although there tends to be a moderate increase of from 4 to 5 mg./day with the phenothiazine compounds as well as with carisoprodol, a larger number of observations would be required to ascertain the significance of this rise. Administration of reserpine resulted in a fall of approximately 5 mg./day in basal levels, again a finding of limited significance. An analysis of the diurnal secretory pattern of 17-KGS, which normally is less during the nocturnal 12 hours than during the daytime, revealed no striking deviation from normal patterns except in 3 subjects given carisoprodol, in whom diurnal fluctuation seemed to disappear. Except for this small difference, the effects of carisoprodol, meprobamate, chlorpromazine, and nialamide upon basal adrenocortical activity would appear to be of the same nature and order of magnitude.

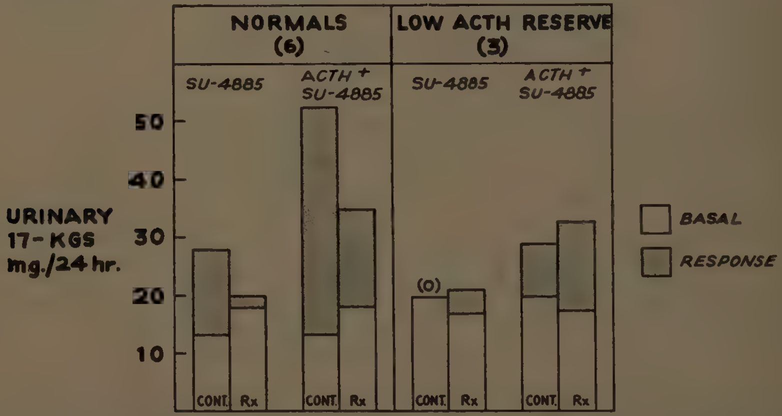

FIGURE 9. Lack of effect of chlorpromazine upon pituitary or adrenal function in patients with low ACTH reserve (unresponsive to SU-4885).

Four of the 5 drugs studied caused a significant reduction in the response to SU-4885, as compared to control observations. Whereas studies prior to treatment demonstrated a doubling of urinary 17-KGS in response to SU-4885, this rise was decreased approximately 59 per cent in patients treated with the phenothiazine compounds, carisoprodol, meprobamate, and nialamide. In the case of the latter three drugs, an effect upon pituitary-adrenal responsiveness has not been reported previously. By contrast, reserpine had no effect upon the rise above control levels normally seen following the administration of SU-4885.

These observations call for a decision as to whether the inhibitory drugs act centrally to suppress ACTH secretion or whether they interfere with the peripheral action of ACTH upon the adrenal cortex. In the hope of evaluating the responsiveness of the adrenal cortices directly, tests were carried out in which SU-4885 was given together with exogenous ACTH. It soon became apparent that treatment for more than 3 days with the suppressant drugs resulted in a fall in adrenocortical responsiveness that was of the same order of magnitude as that observed with SU-4885 alone. A similar inhibitory effect of chlorpromazine upon response to both typhoid vaccine and intramuscular

ACTH has been reported recently by Fotherby *et al.*[15] These workers postulated that chlorpromazine acted directly upon the adrenal to lower its responsiveness. However, a secondary decline in adrenocortical responsiveness, resulting from either central inhibition of the hypothalamus or sufficiently intense or prolonged pituitary suppression, could also explain the data. A reduction in adrenal sensitivity to administered ACTH has been observed experimentally with hypothalamic lesions involving the median eminence (W. F. Ganong, personal communication). Pituitary failure commonly results in an impairment of the steroidogenic response to exogenous corticotropin.[16] The dependence of the functional integrity of the adrenal upon periodic bursts of corticotropin discharged from the pituitary has been emphasized in recent studies carried out by Nugent *et al.*,[17] in which it was found that small priming doses of ACTH markedly potentiate the steroidogenesis elicited by large doses of ACTH given subsequently.

In addition to these findings, which indicate the intimate relationship between adrenal secretory capacity and changes in corticotropin secretion, it has been suggested by other workers that, in the experimental animal, chlorpromazine impairs adrenal function by a central, rather than a peripheral, action. The findings of Hamburger,[18] of Sevy *et al.*,[19] and of Olling and de Wied[7] indicate that, in the rodent, chlorpromazine suppresses corticotropin release in response to various stimuli via a central inhibitory action. The latter two groups also demonstrated that chlorpromazine has no direct effect upon the rat adrenal in so far as the ascorbic acid-depleting action of exogenous ACTH is concerned. Likewise, chlorpromazine does not lower the secretion of Porter-Silber chromogens by the canine adrenal in response to intravenous ACTH.[20] Some of our findings in man, while not conclusively excluding a direct effect of chlorpromazine upon the adrenal cortices, tend to favor a central site of action for the reduction in adrenal secretory function observed with this drug. None of the agents tested interfered with the responsiveness of the adrenal to mechanisms regulating normal basal activity, yet the capacity to increase secretory function above this level was reduced in subjects normally responsive to SU-4885. However, in those patients already limited in pituitary ACTH reserve who were given chlorpromazine, not only was basal activity unaffected by treatment, but response to SU-4885 administered with exogenous ACTH also remained unchanged. This would appear to make a direct, nonselective action of the drug upon the adrenal cortex unlikely. These findings suggest further that in these patients the central mechanism regulating corticotropin secretion had become fixed at a level sufficient to maintain basal activity and that chlorpromazine was ineffectual in reducing this level still further.

The present studies support the view advanced by Harris[21] regarding the dual nature of the mechanisms regulating corticotropin secretion, one component of the duality being concerned with maintaining basal as well as diurnal fluctuations in adrenocortical function and the other with abrupt increases in secretory activity in response to various stimuli. Thus the pharmacological inhibitors tested appear selectively to impair this latter mechanism only, in so far as response to SU-4885 is concerned. Further studies are required with respect to the effect of these drugs on the sensitivity of the mechanism to other stimuli, such as traumatic stress.

These studies also raise speculation regarding the role of norepinephrine and serotonin in the central regulation of corticotropin secretion. Brodie and his co-workers[22,23] recently have summarized the evidence indicating that psychotropic drugs act within the brain upon one or the other of these catechol amines to achieve their central nervous system effects. Norepinephrine in particular has been shown to be capable of eliciting corticotropin release[24] and, as recently reported by Sayers,[25] it can increase the titer of circulating ACTH in the adrenalectomized, decerebrate rat, presumably by an action upon hypothalamic centers. Chlorpromazine, by blocking the excitatory influence of norepinephrine upon certain effector sites,[26] perhaps those concerned with corticotropin release in the hypothalamus, may thus impair response to the stimulus provided by SU-4885. Nialamide, by contrast, is a potent inhibitor of monoamine oxidase[27] and, like iproniazid, it probably not only antagonizes norepinephrine directly,[28] but also causes a preferential accumulation of brain serotonin.[29] The effect of this amine within the autonomic nervous system, as postulated by Brodie and Shore,[22] is to counter the action of norepinephrine. If norepinephrine plays a physiological role in causing corticotropin discharge, the action of nialamide in suppressing response to SU-4885 may reside, as in the case of chlorpromazine, in its ability to antagonize norepinephrine. Reserpine differs from both chlorpromazine and nialamide in that it affects serotonin[30] as well as norepinephrine.[31] This agent prevents the storage of these amines by impairing intracellular binding, resulting in their constant synthesis and release by brain cells. Inasmuch as both serotonin and norepinephrine continue to be available physiologically, the failure of reserpine to antagonize norepinephrine activity significantly could be responsible for its inability to influence response to SU-4885. The suppressant effect of carisoprodol and meprobamate upon this response cannot be explained at present on the basis of neurohormonal mediator effects. However, the selective action of meprobamate on thalamic interneurons,[32] as well as the analgesic and anticholinergic properties of carisoprodol,[33] suggest possible and as yet unexplored mechanisms within the central nervous system by which drugs may modify pituitary-adrenal function.

Summary

A reproducible release of anterior pituitary corticotropin by the intravenous administration of SU-4885 (30 mg./kg. over a 4-hour period) will normally lead to a twofold rise in urinary 17-ketogenic steroids (17-KGS). Various nonnarcotic central nervous system analgesic and psychotropic drugs that do not affect the basal output of 17-KGS significantly have been shown to impair the rise in 17-KGS normally seen with SU-4885 administration. Essentially similar results were obtained with chlorpromazine, carisoprodol, nialamide, and meprobamate in clinically effective dosages. Reserpine had no such effects. Experimental findings supporting a central corticotropin suppressant activity of these agents have been cited.

Acknowledgments

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References

1. Hume, D. M. 1949. The role of the hypothalamus in the pituitary-adrenal cortical response to stress. J. Clin. Invest. **28:** 790.
2. Woodbury, D. M. 1958. Relation between the adrenal cortex and the central nervous system. Pharmacol. Rev. **10:** 275.
3. Ganong, W. F. & P. H. Forsham. 1960. Adenohypophysis and adrenal cortex. Ann. Rev. Physiol. In press.
4. Munson, P. L. & F. N. Briggs. 1955. The mechanism of stimulation of ACTH secretion. Recent Progr. in Hormone Research. **11:** 83.
5. Hume, D. M. & G. J. Wittenstein. 1950. The relationship of the hypothalamus to pituitary-adrenocortical function. Proc. First Clin. ACTH Conf.: 134–147.
6. Costa, P. J., G. H. Glaser & D. D. Bennycastle. 1955. Effects of diphenylhydantoin (Dilantin) on adrenal cortical function. Arch. Neurol. Psychiat. **74:** 88.
7. Olling, C. C. J. & D. de Wied. 1956. Inhibition of the release of corticotrophin from the hypophysis by chlorpromazine. Acta Endocrinol. **22:** 283.
8. Wells, H., F. N. Briggs & P. L. Munson. 1956. The inhibitory effect of reserpine on ACTH secretion in response to stressful stimuli. Endocrinology. **59:** 571.
9. Christy, N. P., M. Knight, D. Lengson & J. W. Jailer. 1956. Inhibition by chlorpromazine of the adrenocortical response to insulin hypoglycemia. J. Clin. Endocrinol. **16:** 913.
10. Gold, E. M., V. C. DiRaimondo & P. H. Forsham. 1960. Quantitation of pituitary corticotropin reserve in man by use of an adrenocortical 11-beta hydroxylase inhibitor (SU-4885). Metabolism. **9:** 3.
11. Liddle, G. W., D. Island, E. M. Lance & A. P. Harris. 1958. Alterations of adrenal steroid patterns in man resulting from treatment with a chemical inhibitor of 11-beta hydroxylation. J. Clin. Endocrinol. and Metabolism. **18:** 906.
12. Jenkins, J. S., J. W. Meakin, D. H. Nelson & G. W. Thorn. 1958. Inhibition of adrenal steroid 11-oxygenation in the dog. Science. **128:** 478.
13. Gold, E. M. & P. Starr. 1959. Urinary excretion of 17-ketogenic steroids in normal subjects before and after stimulation with intramuscular zinc-ACTH. J. Clin. Endocrinol. and Metabolism. **19:** 907.
14. Norymberski, J. K. 1952. Determination of urinary corticosteroids. Nature. **170:** 1074.
15. Fotherby, K., A. D. Forrest & S. G. Laverty. 1959. The effect of chlorpromazine on adrenocortical function. Acta Endocrinol. **32:** 425.
16. Laidlaw, J. C., W. J. Reddy, D. Jenkins, N. Abu Haydar, A. E. Renold & G. W. Thorn. 1955. Advances in the diagnosis of altered states of adrenocortical function. New Engl. J. Med. **253:** 747.
17. Nugent, C. A., K. Eik-Nes, L. T. Samuels & F. H. Tyler. 1959. Response of plasma levels of 17-OHCS to prolonged infusions of small amounts of ACTH. J. Clin. Endocrinol. and Metabolism. **19:** 334.
18. Hamburger, C. 1955. Substitution of hypophysectomy by the administration of chlorpromazine in the assay of corticotrophin. Acta Endocrinol. **20:** 383.
19. Sevy, R. W., E. A. Ohler & A. Weiner. 1957. Effect of chlorpromazine on stress induced adrenal ascorbic acid depletion. Endocrinology. **61:** 45.
20. Ganong, W. F. & D. Betz. 1960. The effect of chlorpromazine on pituitary-adrenal function in the dog (abstract). 1st Intern. Congr. of Endocrinol. Copenhagen, Denmark.
21. Harris, G. W. 1955. Neural Control of the Pituitary Gland. Arnold. London, England.
22. Brodie, B. B. & P. A. Shore. 1957. Concept for role of serotonin and norepinephrine as chemical mediators in brain. Ann. N. Y. Acad. Sci. **66**(3): 631.
23. Brodie, B. B., D. J. Prockop & P. A. Shore. 1958. Interpretation of action of psychotropic drugs. Postgrad. Med. **24:** 296.
24. Casentini, S., A. De Poli, S. Hukovic & L. Martini. 1959. Studies on control of corticotrophin release. Endocrinology. **64:** 483.
25. Sayers, G. 1957. Factors influencing the level of ACTH in the blood. *In* Hormones in Blood. Ciba Foundation Colloquia on Endocrinology. **11:** 138. G. E. W. Wolstenholme & E. C. Millar, Eds. Little, Brown. Boston, Mass.
26. Rothballer, A. B. 1959. The effects of catecholamine on the central nervous system. Pharmacol. Rev. **11:** 494.

27. Rowe, R. P., B. M. Bloom, S. Y. P'an & K. F. Finger. 1959. Pharmacological studies with nialamide, a new antidepressant agent. Proc. Soc. Exptl. Biol. Med. **101:** 832.
28. Griesemer, E. C., C. A. Dragstedt, J. A. Wells & E. A. Zeller. 1955. Adrenergic blockade by iproniazid. Experientia. **11:** 182.
29. Sjoerdsma, A., T. E. Smith, T. D. Stevenson & S. Udenfriend. 1955. Metabolism of 5-hydroxytryptamine (serotonin) by monoamine oxidase. Proc. Soc. Exptl. Biol. Med. **89:** 36.
30. Pletscher, A., P. A. Shore & B. B. Brodie. 1955. Serotonin release as a possible mechanism of reserpine action. Science. **122:** 374.
31. Shore, A. & B. B. Brodie. 1957. Influence of various drugs on serotonin and norepinephrine in the brain. *In* Psychotropic Drugs. : 423. S. Gorattini and V. Ghetti, Eds. Elsevier. New York, N. Y.
32. Berger, F. M. 1954. The pharmacological properties of 2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate (Miltown), a new interneuronal blocking agent. J. Pharmacol. Exptl. Therap. **112:** 413.
33. Berger, F. M., M. Kletzkin, B. J. Ludwig, S. Margolin & L. S. Powell. 1959. Unusual muscle relaxant and analgesic properties of N-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate (carisoprodol). J. Pharmacol. Exptl. Therap. **127:** 66.

PHARMACOLOGY OF PHENYRAMIDOL (IN511) WITH EMPHASIS ON ANALGESIC AND MUSCLE-RELAXANT EFFECTS*

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Experimental studies with animals[1] have demonstrated that phenyramidol has two primary actions: it produces (1) analgesic and (2) muscle-relaxant effects. These effects were evident at doses far below toxic levels and were found after either parenteral or oral administration of the drug. To facilitate evaluation and to clarify the degrees of activity found for phenyramidol, these results are here compared with those obtained in our laboratory for known drugs under the same conditions and with the same tests. Since phenyramidol was the only drug studied that produced both measurable analgesia and muscle relaxation, it was necessary to employ a different group of known or standard drugs to compare each effect. The drugs used for comparison of analgesic activity were codeine, *d*-propoxyphene, carisoprodol, and aspirin. Mephenesin, meprobamate, and carisoprodol were utilized for evaluation of relative muscle-relaxant activity.

As a chemical entity, phenyramidol is unique in that it is unrelated to and does not resemble any other currently available analgesic or muscle-relaxant type of compound (TABLE 1). Phenyramidol is a white, crystalline, water-soluble salt that forms slightly acid aqueous solutions. It is quite stable either in the pure state or in solution under a variety of temperature or *p*H conditions. Strong alkalies added to aqueous solutions of the drug lead to precipitation of the base form of the drug. The drug has a broad range of chemical compatibilities.

Analgesic Activity

Tests on mice. One method used was based on reactions to a radiant-heat stimulus produced by a "conduction dolorimeter." Although this instrument was designed to produce the stimulus by application of heat to the tail of a mouse, it was found that utilization of the hind foot as a test organ resulted in more consistent reaction times. The degree of analgesic activity was related to the percentage increase in the stimulus-response time lag. Groups of 20 mice treated with the drug were compared with control groups tested concurrently. Evaluation of the data obtained from 1200 untreated control mice (60 groups) showed that an average increase in reaction time-lag of more than 14 per cent for a group of 20 mice would be highly significant.

The results obtained with this procedure are shown in FIGURE 1. Results with various routes of administration and various drugs—codeine, *d*-propoxyphene, carisoprodol, and aspirin—are listed in the table for reference comparison. As is evident from these results, phenyramidol produced a significant degree of analgesia when administered either parenterally or orally. As an analgesic, phenyramidol appeared to be comparable to codeine and was superior to *d*-propoxyphene, carisoprodol, and aspirin. In fact, by this test, it was not possible to demonstrate any analgesic effects in animals with the latter two drugs.

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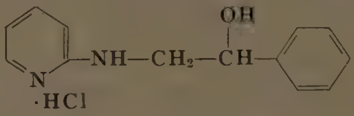
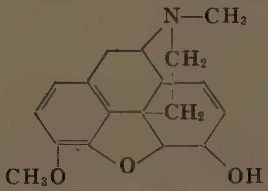
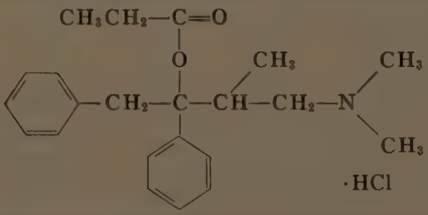
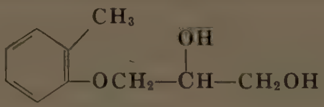
* Phenyramidol, 2-(β-hydroxyphenethylamino)pyridine hydrochloride, is also known as Analexin.

A second test method involving mice[2] was based on the suppression of the writhing reaction characteristically produced when mice are injected intraperitoneally with *p*-phenylquinone. Aspirin, as well as codeine and other stronger analgesic drugs, will suppress this reaction.[2] Phenyramidol also was found to be effective when evaluated by this method, although somewhat less so than codeine. (The oral ED_{50} dose of phenyramidol is 65 mg./kg., as compared with 40 mg./kg. for codeine and 120 mg./kg. for aspirin.)

TABLE 1

STRUCTURAL FORMULAS AND ACUTE TOXICITY VALUES IN MICE

Drug	Structural formula	LD_{50} (mg./kg.)		
		I.V.	I.P.	P.O.
Phenyramidol		124	450	2425
Codeine	 (sulfate)	87	200	
d-Propoxyphene	 CH₃CH₂—C=O O CH₃ CH₃ —CH₂—C—CH—CH₂—N CH₃ ·HCl	25	128	
Mephenesin		250	570	

Tests on rabbits. These tests[3] were based on suppression of the response to pain resulting from electric stimulation of the tooth pulp. To produce the pain, a hole was drilled in each of the two upper teeth, shielded spring electrodes were inserted, and square-wave shocks were given through these electrodes. The maximum duration of each shock was 5 sec. with intervals of 30 sec. between shocks. The voltage was varied while other settings (frequency

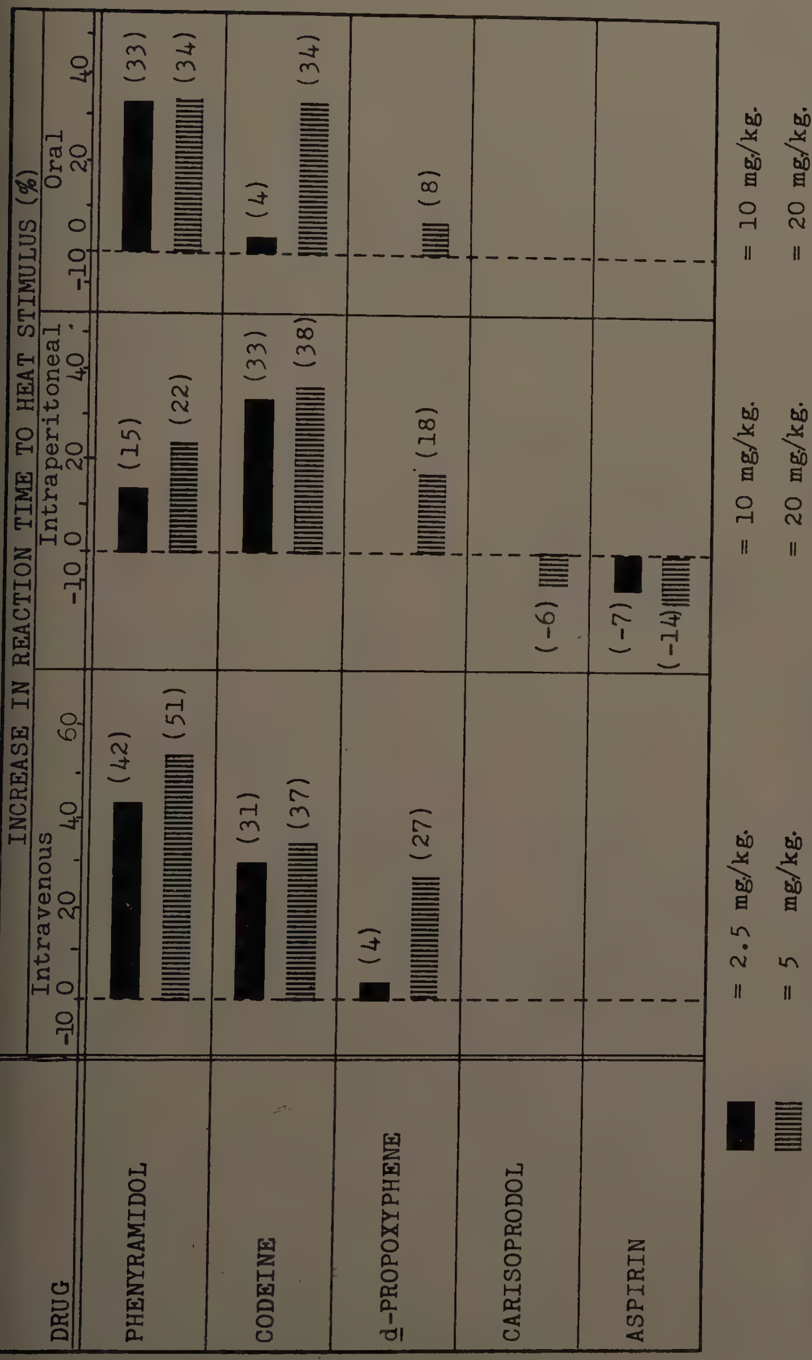


Figure 1. Relative analgesic activities in mice stimulated with radiant heat. Figures in parentheses denote actual percentage increases in reaction times; increases greater than 14 per cent are highly significant ($p < 0.01$). Aspirin in acacia suspension was given in doses of 200 and 400 mg./kg.

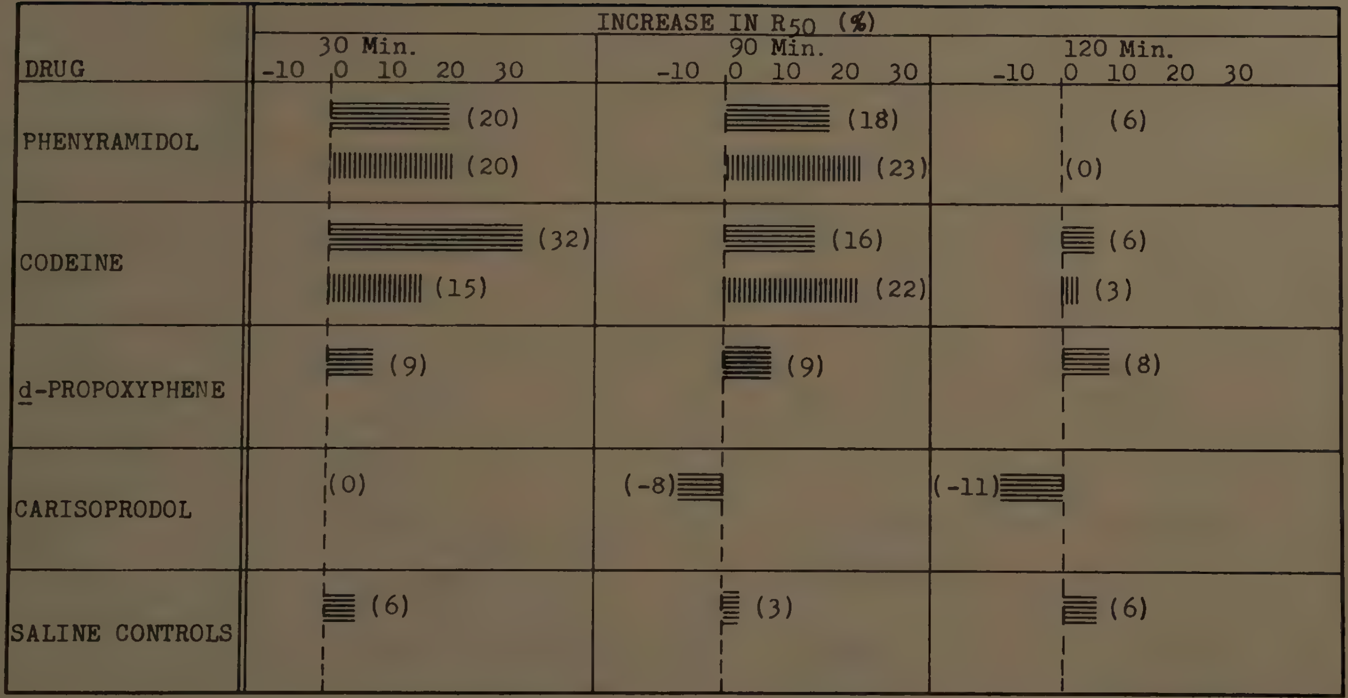


FIGURE 2. Relative analgesic activities in rabbits: tooth pulp stimulation. Percentage increase in R_{50} (the voltage, calculated from the data obtained, at which the animals should respond 50 per cent of the time) 30, 90, and 120 min. after stimulation. The figures in parentheses are actual percentage values. Dosages: horizontally striped bars, 5 mg./kg. intravenously; vertically striped bars, 10 mg./kg. orally.

of pulses, and so forth) remained constant. When the stimulus reached a painful intensity, the rabbit reacted by wiggling its nose and upper lip. All determinations were carried out in quadruplicate and from the data obtained, calculations were made of R_{50}, the voltage at which the rabbit responded to pain 50 per cent of the time. Each animal was tested prior to and 30, 90, and 150 min. after administration of the drug. The degree of analgesic activity shown by a drug was based on the percentage difference between the pre- and posttreatment values of R_{50}.

The results with phenyramidol, codeine, *d*-propoxyphene, carisoprodol, and saline (placebo) are shown in FIGURE 2. The placebo results indicated that increases of 6 per cent or less in post- over pretreatment values of R_{50} were not significant. Phenyramidol, when tested by this method, demonstrated significant analgesic activity after being administered either intravenously or orally.

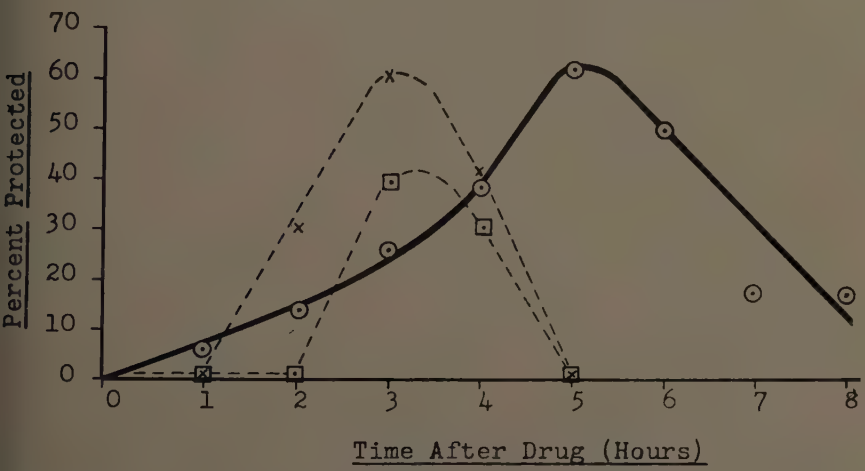


FIGURE 3. Effects on silver-nitrate induced pain of oral administration of 20 mg./kg. phenyramidol, ⊙; 150 mg./kg. carisoprodol, ⊡; and 300 mg./kg. carisoprodol, ×.

Again, in the over-all analysis of the data, phenyramidol compared favorably with codeine and was superior to *d*-propoxyphene and carisoprodol. This test, as well as that involving the heat stimulus in the mouse, yielded no evidence of analgesic activity for carisoprodol. The difficulty of determining an analgesic effect of carisoprodol in animals has been reported elsewhere by Berger and his colleagues.[4]

Tests on rats. Silver nitrate injected into the ankle joint of a rat's hind leg causes a painful edematous inflammation within 18 hours.[4,7] Flexion of the joint produces a pain reaction, indicated by a cry from the animal. The drugs being tested were administered orally, and assessment of pain or analgesia was made at hourly intervals for 5 to 8 hours. Absence of a cry response on flexion of the joint was taken as an indication of analgesia.

Inasmuch as carisoprodol had been reported[4] to be effective in this respect, it was tested concurrently with phenyramidol. The results obtained are shown graphically in FIGURE 3. The effects of carisoprodol at the doses indicated are essentially the same as those reported by Berger *et al.* with regard to the maximum degree of response. Phenyramidol, at less than one tenth the dose of carisoprodol, produced a comparable degree of analgesia. Although the onset of action of phenyramidol was evident within 1 to 2 hours, the effect reached a peak only 5 hours after administration, and lasted for 8 hours or more.

Apparently, the inflammation itself was not affected; this is in agreement with results of standard anti-inflammatory testing procedures.

Muscle-Relaxant Activity

Skeletal muscle relaxation can be induced by several mechanisms. Preliminary investigations indicated that the relaxation induced by phenyramidol was the result of an interneuronal blocking action.

The interneuronal blocking activity of phenyramidol was evaluated and compared with that of other drugs by utilizing two reflexes, both of which require polysynaptic transmission of impulses. The reflexes used were the flexor (hind-leg twitch) and the linguomandibular (jaw closure). Experimental preparations consisted of both pentobarbital-anesthetized and decerebrate dogs. Drugs used for comparison with phenyramidol were mephenesin, meprobamate, and carisoprodol, for the reason that interneuronal blocking activity had been described previously for the first two drugs and inferred for the latter.

The results obtained with pentobarbital-anesthetized and decerebrate dogs are shown in FIGURES 4 and 5, respectively. While the effects on the two dog preparations were quantitatively somewhat different, qualitatively the results were similar except that carisoprodol showed different responses in the two experimental preparations.

Phenyramidol elicited a dose response and was effective in depressing both reflexes tested. In comparison with the other drugs at the same dose, phenyramidol proved to be the most active relaxant. Carisoprodol produced a depression of the flexor reflex in the pentobarbital-anesthetized dogs; the linguomandibular reflex in these dogs, however, and both reflexes in decerebrate dogs were stimulated by the drug. This apparent discrepancy may have resulted from a potentiation of anesthesia by carisoprodol, since it has been demonstrated that administration of additional pentobarbital will often depress the flexor reflex. Meprobamate given to the decerebrate dogs did not show any blocking effects at the dose employed. It should be mentioned, however, that this dose is less than that reported to produce blockade of the reflexes in the cat (for example, 30 to 40 mg./kg. I.V.).[5]

Tests providing less specific measures of muscle-relaxant action were carried out with mice. The effect of drugs on the righting reflex was tested, and the results were expressed as the dose (in mg./kg.) that caused a loss of righting reflex or paralysis in 50 per cent of the animals (PD_{50}). This test also gives positive results for drugs with curarimimetic or hypnotic (sedative) properties. TABLE 2 shows the PD_{50} values obtained for phenyramidol, mephenesin, carisoprodol, and meprobamate compared with the corresponding acute toxicity (LD_{50}) values. As is evident from the results shown in the table, there is no direct correlation between the effect on the righting reflex and interneuronal blocking activity, for the drug having the greatest LD_{50}/PD_{50} ratio, carisoprodol, proved to be a relatively poor interneuronal blocking agent.

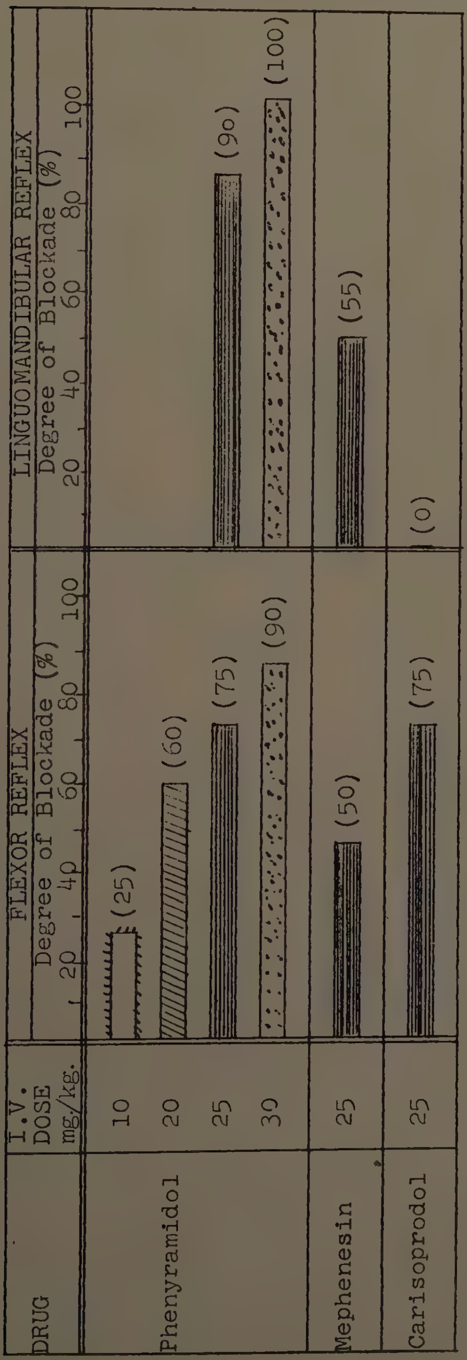


FIGURE 4. Relative interneuronal blocking effects in pentobarbital-anesthetized dogs. Figures in parentheses indicate actual percentage values; (0) indicates increased muscular twitch.

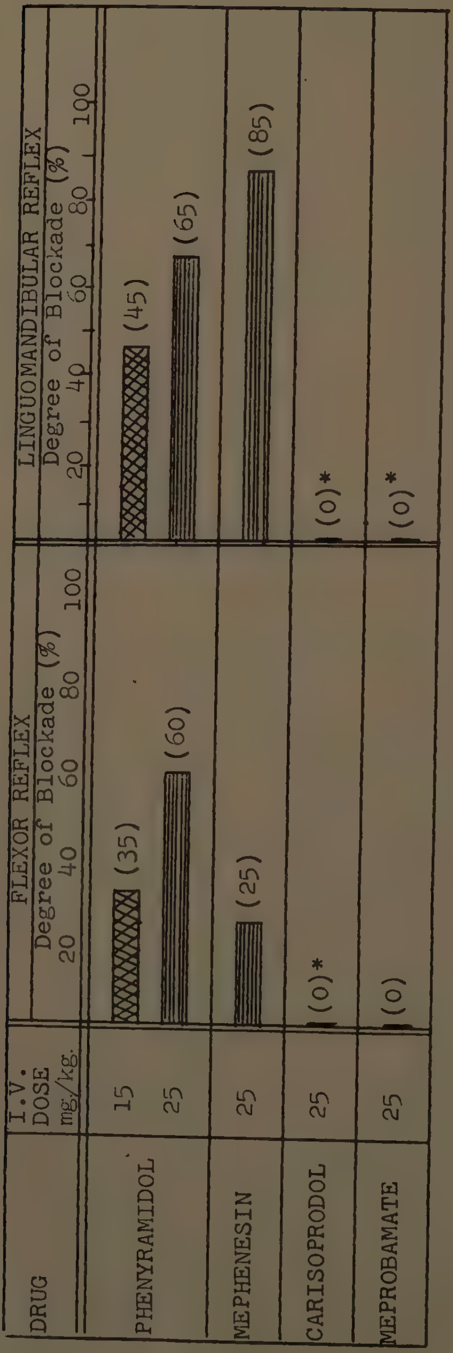


FIGURE 5. Relative interneuronal blocking effects in decerebrate dogs. Figures in parentheses indicate actual percentage values; (0)* indicates increased muscle twitch.

Phenyramidol proved to be an effective muscle relaxant for other unanesthetized animals as well (for example, dogs, cats, and monkeys). The degree of relaxation appeared to be a function of the dosage employed; there was no evidence of tolerance to this effect even when the drug was administered intravenously once daily for 90 days (for example, to dogs, 20 mg./kg. I.V. once daily).

Other Effects on the Central Nervous System

Several testing procedures were used to ascertain whether phenyramidol in reasonable doses would produce other effects on the central nervous system such as are found occasionally with other analgesic or muscle-relaxant drugs. Two such procedures were used to determine the effects of drugs on voluntary motor activity and duration of hexobarbital anesthesia in mice. In the former determination an activity chamber was used in which motor activity was measured by the number of times a light beam was broken in a 60-min. period. The results obtained for phenyramidol, mephenesin, meprobamate, and carisoprodol are shown in TABLE 3.

TABLE 2

RELATIVE ACUTE TOXICITY (LD_{50}) AND RIGHTING REFLEX (PD_{50}) VALUES IN MICE

Drug	Route	Righting reflex PD_{50} (mg./kg.)	Acute toxity LD_{50} (mg./kg.)	LD_{50}/PD_{50}
Phenyramidol	I.V. I.P.	30 185	124 450	4.1 2.4
Mephenesin	I.P.	145 (178)*	570 (610)	3.9
Carisoprodol†	I.P.	130 (165)	750 (980)	5.8
Meprobamate‡	I.P.	285 (235)	600 (800)	2.1

* Figures in parentheses indicate values reported in the literature.
† In 50 per cent Carbowax 200 solution.
‡ In 2 per cent acacia suspension.

With regard to potentiation of hexobarbital, phenyramidol and all the other drugs used for comparison caused some increase in the duration of anesthesia; however, none of these drugs would be considered potent relative to others such as chlorpromazine. Phenyramidol administered intraperitoneally at 25 mg./kg. did not appear to cause any depression of motor activity in mice. The apparent depression observed after administration of 50 mg./kg. could be a result of its muscle-relaxant action. Meprobamate had no effect on motor activity in doses up to 100 mg./kg., and carisoprodol gave inconsistent responses. The apparently inconsistent responses to doses of carisoprodol are probably a result of the fact that this drug caused an initial increase in motor activity followed by a decrease; the larger the dose, the greater was the initial increase in motor activity.

Other tests for effects on the central nervous system and the general results obtained were as follows:

(1) Anticonvulsant activity (for instance, antiepileptic effects). Convul-

sions were induced in mice electrically and chemically (with pentylenetetrazole, strychnine, and nicotine); phenyramidol in doses as high as 100 mg./kg. I.P. offered no protection against the convulsions.

(2) Effect on central thermoregulatory centers. Phenyramidol had no effect on the normal body temperature of unanesthetized rabbits.

(3) Antiemetic activity. On the basis of its antagonism to apomorphine-induced emesis, phenyramidol is inactive.

Thus phenyramidol appears to have little if any effect on the central nervous system other than analgesic and interneuronal blocking actions.

TABLE 3

EFFECTS ON HEXOBARBITAL ANESTHESIA AND VOLUNTARY MOTOR ACTIVITY IN MICE

Drug	I.P. dose (mg./kg.)	Hexobarbital anesthesia*			Voluntary motor activity		
		Duration, min.		D/C	60-Min. counts		D/C
		Control (C)	Drug (D)		Control	Drug	
Phenyramidol	25	7	12	1.7	352	356	1.01
	50	6	10	1.7	304	130	0.43
Mephenesin	50	6	9	1.5			
	100	6	13	2.2			
Meprobamate	50	7	9	1.3	252	224	0.90
	100	7	19	2.7	340	326	0.95
Carisoprodol	50	7	9	1.3	489	285	0.58
	100	10	13	1.3	328	372	1.12

* Administered intravenously, 50 mg./kg., 20 min. after saline or drug.

Other Pharmacological Properties

Phenyramidol, while relatively weak when administered parenterally, did produce a moderate degree of local anesthesia in humans when applied topically to the tongue. As determined by experimentally produced acute and chronic inflammatory conditions in rats,[6] phenyramidol is inactive as an anti-inflammatory agent per se, but it has no deleterious influence on the beneficial effects produced by the salicylates or steroids. Phenyramidol is weak as a smooth muscle relaxant, as determined by tests on the isolated guinea pig ileum with acetylcholine, histamine, and barium chloride as spasmogenic agents. The effects of phenyramidol on the cardiovascular system, as determined by intravenous administration in pentobarbital-anesthetized dogs, are such that, at doses greater than effective analgesic and muscle-relaxant doses, a slight, transient drop in blood pressure is occasionally produced, unaccompanied by observable effects on heart action. Evidence for any direct action on the peripheral or coronary arteries is also lacking.

Metabolism and Excretion

Phenyramidol is not excreted unchanged in the urine. Radioactive tracer studies have indicated that some is excreted in the urine as a metabolic product(s) for a considerable period of time after oral administration. Further investigations are contemplated regarding the metabolism, distribution, and fate of phenyramidol.

Toxicity Studies

Phenyramidol is a relatively nontoxic drug, especially when given in the doses required for effective analgesic and muscle-relaxant actions. Its low toxicity is also apparent when its acute toxicity values are compared with those for other analgesic or muscle-relaxant drugs (TABLE 4).

Long-term parenteral (90-day) and oral (6 to 12 months) toxicity studies have been conducted with mice, rats, and dogs. Phenyramidol was administered in several doses ranging from the approximate therapeutic level to doses 40 times that found to be effective. Even in the cases where this maximum dose was administered daily over a 12-month period, there was no evidence of drug-induced toxicity as based on monthly blood studies, daily observation, weight gain, and post-mortem macroscopic and microscopic examination of he organs and tissues.

TABLE 4
ACUTE TOXICITY IN MICE

	Acute (24-hour) toxicity, LD$_{50}$ (mg./kg.)		
	Intravenous	Intraperitoneal	Oral
Phenyramidol	124	450	2425
Codeine	87	200	
d-Propoxyphene	25	128	
Mephenesin	250	570	
Carisoprodol[4]	165	980	2340
Meprobamate[4]	482	800	1100

Summary

Phenyramidol is a new drug unique in its biological effects in that it possesses neasurable analgesic as well as muscle-relaxant properties. Of equal imporance is the fact that other central effects occasionally observed with other nalgesic or muscle-relaxant drugs (such as sedation, euphoria, and mental onfusion) have not been apparent in pharmacological studies. The analgesic ctivity of phenyramidol is of the order of codeine, and the mechanism of the nuscle relaxation (interneuronal blockade) produced by this drug is desirable n that such a mechanism can abolish abnormal muscle tone without impairing ormal neuromuscular function.

The nature of pain, and also the cause of a painful state, can be very complex. or example, while pain can be, and very often is, partly or entirely a result f muscular spasm, in many instances where the pain is not directly associated vith a muscular spasm it is exaggerated or intensified by an accompanying nuscle tension. Thus, as has been recognized, combined analgesic and muscleelaxant actions will very often be more effective and beneficial in overcoming the total pain experience than will either of these actions alone. Phenyramidol, a single chemical entity, uniquely provides such a combination of effects.

References

1. O'Dell, T. B., L. R. Wilson, M. D. Napoli, H. D. White & J. H. Mirsky. 1960. Pharmacology of a series of new 2-substituted pyridine derivatives with emphasis on their analgesic and interneuronal blocking properties. J. Pharmacol. Exptl. Therap. **128:** 65–74.
2. Siegmund, E., R. Cadmus & G. Lu. 1957. A method for evaluating both non-narcotic and narcotic analgesics. Proc. Soc. Exptl. Biol. Med. **95:** 729–731.
3. Frisch, A. & M. Dolivo. 1953. Evaluation of analgesics by animal experiments. Helv. Physiol. Acta. **11:** 305–322.
4. Berger, F. M., M. Kletzkin, B. J. Ludwig, S. Margolin & L. S. Powell. 1959. Unusual muscle relaxant and analgesic properties of N-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate (carisoprodol). J. Pharmacol. Exptl. Therap. **127:** 66–74.
5. Berger, F. M. 1954. The pharmacological properties of 2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate (Miltown), a new interneuronal blocking agent. J. Pharmacol. Exptl. Therap. **112:** 413–423.
6. Coutu, L. L., R. J. Gareau & S. Ducommun. 1953. Morphological study of experimental arthritis in the rat treated with cortisone or desoxycorticosterone. Rev. can. biol. **12:** 40–67.
7. LaBelle, A. & R. Tislow. 1950. A method of evaluating analgesics of the antiarthralgic type in the laboratory animal. J. Pharmacol. Exptl. Therap. **98:** 19.

UTILIZATION OF PHENYRAMIDOL HYDROCHLORIDE FOR CLINICAL ANALGESIA

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The rapidity of development of new compounds for the relief of pain has emphasized our needs for controlled appraisal techniques. The clinical utilization of phenyramidol hydrochloride as presented in this report will depict the various steps that were undertaken and are still in progress for the determination of its analgesic effectiveness.

Clinical appraisal must begin with confirmation of the analgesic action noted with animal testing. O'Dell and his co-workers[1] investigated a series of 2-substituted pyridine derivatives and noted that the 2(beta-hydroxy phenethyl amino)-pyridine, now known as phenyramidol, possessed analgesic properties comparable to those of codeine and superior to those of dextropropoxphene, and an interneuronal blocking activity greater than that shown by mephenesin. Preliminary studies by our laboratory in patients with varying types and degrees of pain confirmed to our satisfaction that the preparation had an analgesic action of moderate potency. This first step or "across-the-board" appraisal indicated possible potency and clinical conditions that might be subject to more intensive investigation. This important step is often overlooked and confused with analgesic effectiveness. The latter represents clinical utilization and suggests satisfactory control of pain under conditions of use, with minimal occurrence of untoward reactions. Many preparations possess analgesic properties, but cannot be recommended for clinical purposes because of cumulative toxicity or untoward reactions that become evident only under actual use.

The second step is the determination of the value of the new compound, not for its analgesic powers, which are already known, but for the satisfactory control of a painful state according to the "ideal" criteria demanded of such a medication.[2] As indicated on several previous occasions,[3-5] the evaluation of new drugs must consider and, as closely as possible, duplicate the conditions under which these drugs will actually be used by the general practioner. It s my contention that any artificial, complex method of drug appraisal not only limits the conclusions to the particular study design, but also that these conclusions are often at variance with actual clinical use. The clinical utilization of phenyramidol by our laboratory was thus investigated by the method of comparative clinical appraisal with standard medications.

Since the ambulatory patient with moderately severe pain represents a very large segment of clinical conditions, the evaluation of phenyramidol ncluded 2 groups of such patients. The first group consisted of 118 patients with musculoskeletal disorders. The second group, consisting of 59 patients, had various types of chronic painful states usually encountered, other than arthritis. To complete the survey, an additional group of 39 hospitalized patients who required analgesia for relief of pain secondary to various medical and surgical conditions was also included.

The first ambulatory group of 118 patients with musculoskeletal conditions was studied according to 3 dosage schemes (TABLE 1), thus accounting for 155 observation periods. Dosages of 100, 200, and 100 mg., with concomitant 300 mg. of aspirin, were observed in groups of 43, 61, and 51 subjects, respectively. For the basis of comparative clinical testing, similar groups of patients received placebo therapy (2 groups), 600 mg. aspirin (2 groups), and 600 mg. sodium salicylate. All studies were performed concurrently. The majority of patients, when the period of observation for any medication—control, standard, or phenyramidol—was completed, received by randomization any of the other preparations. It was thus possible to study multiple trials with 2 or more of the medications in the same patient. Thus, cross-over observations lent significance to the over-all effectiveness for each medication administered.

TABLE 1

COMPARATIVE ANALGESIC EFFECTIVENESS OF PHENYRAMIDOL HYDROCHLORIDE ORALLY IN AMBULATORY PATIENTS WITH MUSCULOSKELETAL DISORDERS

Medication	No. of patients	Effective		Untoward reactions	
		No. of patients	Per cent	No. of patients	Per cent
Placebo	49	17	34.6	6	12.0
	41	19	46.3	5	12.2
Aspirin (600 mg.)	87	45	51.7	24	27.5
	128	68	53.1	30	23.4
Sodium salicylate (600 mg.)	40	20	50.0	16	40.0
Phenyramidol HCl					
100 mg.	43	23	53.6	8	18.5
200 mg.	61	34	59.0	9	14.9
100 mg. + 300 mg. asp.	51	34	66.6	8	15.7

All medications were administered 4 times daily, and an effort was made to observe each patient for a minimal period of 2 weeks of continuous drug usage. This was possible in 88 per cent of the trials. Forty per cent of the patients continued the medication for 3 to 22 weeks so that it would be possible to note any cumulative toxicity or tolerance.

TABLE 1 summarizes the comparative clinical effectiveness of phenyramidol hydrochloride with placebo therapy, aspirin, and sodium salicylate in ambulatory patients with musculoskeletal disorders. An analgesic response in this and the other groups of patients to be reported included an analysis of degree of pain relief, the occurrence of untoward reactions, and the over-all response for the entire period of observation. A satisfactory clinical control required an unquestioned relief for two or more hours for each drug administration without the occurrence of significant untoward reactions. The occurrence of reactions that interfered with or overshadowed the analgesic response was detrimental to clinical usage, and such a trial was therefore considered to be nonsatisfactory. The over-all response for the entire period of observation was of major importance. Patients with chronic pain require continuous satisfactory relief without cumulative toxicity or tolerance. The results reflect continuous satisfactory control of the patient's painful state and not the effects of an isolated drug administration.

On the basis of these criteria, phenyramidol, with a dosage of 100 mg. 4 times daily, was as effective as 600 mg. of aspirin or sodium salicylate. The 200-mg. dosage was slightly more effective. The 67 per cent effectiveness of the combination of phenyramidol and aspirin suggests synergism or summation.

Table 2 shows the various arthritic conditions that were treated. It is apparent that the combination of phenyramidol and aspirin was most effective for both osteoarthritis and rheumatoid arthritis. Included in the miscellaneous group were patients with gout and shoulder-hand syndrome who did not respond to any dosage scheme. We were not impressed with any specificity of action, such as antirheumatic or anti-inflammatory effects. Two hundred mg. was an effective dosage for patients with osteoarthritis and rheumatoid arthritis, but not for menopausal arthralgia.

Table 2

Satisfactory Analgesia with Phenyramidol Hydrochloride with Various Arthritic Conditions

Diagnosis	Dosage					
	100 mg.		200 mg.		100 mg. + 300 mg. aspirin	
	No. of patients	Per cent	No. of patients	Per cent	No. of patients	Per cent
Osteoarthritis	13 (24)*	54.1	11 (20)	55.0	18 (23)	78.3
Rheumatoid arthritis	5 (13)	37.7	10 (16)	62.5	9 (12)	75.0
Menopausal arthralgia	2 (3)	—	3 (8)	37.5	3 (5)	60.0
Bursitis	2 (2)	—	1 (1)	—	2 (2)	—
Miscellaneous	1 (4)	—	4 (11)	36.3	2 (5)	—

* Figure in parentheses represents number of patients studied with particular dosage.

Untoward reactions were of no significance. Table 3 summarizes their occurrence for each of the phenyramidol dosages. Gastrointestinal irritation such as nausea, with and without vomiting, epigastric pain, and heartburn were noted infrequently. Pruritus with and without a rash occurred in 4 per cent of the patients and subsided promptly upon discontinuation of medication.

In the second group of 59 ambulatory patients with various medical conditions (table 4) the over-all effectiveness of phenyramidol was 61 per cent and the occurrence of untoward reactions 6.8 per cent. The duration of therapy ranged from less than 1 week in 3 instances to 12 weeks. Five subjects received 100 mg. 4 times daily, 50 patients received the 200-mg. dosage, and 4 patients were treated with 400 mg. 4 times daily. Seven patients with the anginal syndrome were treated with phenyramidol in an attempt to note a possible vasodilating action that might decrease the frequency and severity of the chest pain. As the results were unsatisfactory, these 7 patients are excluded. The clinical effectiveness thus becomes 65 per cent. Failure to respond in the miscellaneous group included patients with advanced carcinoma with metastasis, neurofibromatosis, and migraine. Of particular interest was the group of 10 patients with duodenal ulcer, who presented an excellent symptomatic control of their complaints. These patients were previously under treatment with antacids, antispasmodics, and sedatives, with recurrent pain and unsatisfactory control. Phenyramidol, usually administered alone but occasionally with an antacid, resulted in control of 9 of the 10 patients. The other 10 patients with upper gastrointestinal disorders had similar complaints, but no X-ray confirmation of an ulcer. The possibility of an antispasmodic action of phenyramidol is at present under investigation.

TABLE 3

UNTOWARD REACTIONS NOTED WITH PHENYRAMIDOL HYDROCHLORIDE

Untoward reactions	100 mg.	200 mg.	100 mg. + 300 mg. aspirin
Nausea		3	2
Nausea and vomiting	2		1
Epigastric pain	1	1	3
Constipation	1		
Heartburn	2	2	2
Anorexia	1		
Nervousness		1	
Dizziness		1	
Rash and pruritus	3	1	1
No. patients	8 (43)*	9 (61)*	8 (51)*
Per cent	18.5	14.9	15.7

* Figure in parentheses represents number of patients studied with particular dosage.

TABLE 4

EFFECTIVENESS OF PHENYRAMIDOL HYDROCHLORIDE FOR RELIEF OF PAIN IN AMBULATORY PATIENTS WITH MEDICAL CONDITIONS OTHER THAN ARTHRITIS

Condition	No. of patients	Analgesic effectiveness		
		Complete relief	Moderate relief	Per cent satisfactory
Duodenal ulcer	10	7	2	90
Epigastric distress (pylorus spasm, gastritis, etc.)	10	5	2	70
Abdominal distress (flatulence, colic, constipation)	10	4	2	60
Pleuritic pain	2	1	1	—
Cholecystitis	5	1	1	—
Genitourinary (pyelonephritis)	3		3	—
Anginal syndrome	7	1	1	30
Miscellaneous	12	1	4	41
Totals	59	20	16	61 (65.4)*

* Excluding anginal syndrome.

The group of 39 hospitalized patients presented a clinical effectiveness of

66.6 per cent with a dosage of 200 mg. phenyramidol every 4 hours from 1 to 7 days of therapy. Nausea, the only untoward reaction noted, occurred in only 2 patients. The patients who failed to respond included patients with advanced metastatic carcinoma, severe active rheumatoid arthritis, and 1 case of extensive third-degree burns.

Clinical studies with phenyramidol have been in progress by my staff since March 1958. During this time it has become evident that this medication satisfies the majority of the criteria demanded of a moderately potent non-specific analgesic agent. There is no question that the predictability of satisfactory control of a painful state is high and that the occurrence of untoward reactions is low. The resultant analgesia occurred promptly and persisted for at least 3 to 4 hours. Therapeutic doses did not affect the cardiovascular, renal, and respiratory systems and did not result in cumulative toxicity upon the central nervous system, liver, and blood-forming organs.

It is concluded that phenyramidol administered orally is a moderately potent and safe analgesic for acute and chronic pain for both ambulatory and hospitalized patients.

References

1. O'Dell, T. B., L. R. Wilson, M. D. Napoli & J. H. Mirsky. 1959. Federation Proc. **18:** 1694.
2. Batterman, R. C. 1954. J. Am. Med. Assoc. **155:** 965.
3. Batterman, R. C., M. Golbey, A. J. Grossman & P. Leifer. 1957. Am. J. Med. Sci. **234:** 413.
4. Batterman, R. C. & A. J. Grossman. 1955. J. Am. Med. Assoc. **159:** 1619.
5. Batterman, R. C., A. J. Grossman, P. Leifer & G. J. Mouratoff. 1959. Postgrad. Med. **26:** 502.

THE EVALUATION OF NEUROSPASMOLYTIC AGENTS IN MAN BY OBJECTIVE MEANS

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The evaluation of muscle-relaxant agents in man, whether for musculoskeletal or neurological disorders, has heretofore been done essentially on a qualitative basis, quantitative appraisal having been carried out on experimental animals, utilizing various highly refined techniques. This paper offers an approach to the quantitative evaluation of muscle-relaxant therapy in man, with particular emphasis on neurospasmolytic agents.

The studies to be described have been carried out by the Neurological Research Team of the Veterans Administration Outpatient Clinic. Test subjects have been selected from the large group of multiple sclerosis patients known to this clinic, in whom spasticity is a prominent sign and symptom. The patients used in our studies are at a fairly static level of disability, thereby reducing changes due to natural fluctuations of the disease to a minimum.

The method used depends on a cooperative team approach that includes the patient, while at the same time permitting independent functioning of the professional staff within the various categories of the study. Medication is prescribed and dispensed by double-blind administration, with central control remaining in the hands of our chief pharmacist. The three physicians on the team are assigned their respective duties as follows.

The first regulates the maintenance dose of medication, initiates and terminates the double-blind period, interviews the patients, and keeps clinical notes.

The second physician performs clinical examinations and assessments of spasticity on a clinical basis, grading this from 0 to 4 as follows: 0 = no resistance to passive flexion and extension at knee; 1 = slight resistance to passive flexion at knee, without increase in spasticity to extension-flexion thrust; 2 = moderate resistance to passive flexion at knee with moderate degree of increase in spasticity with extension-flexion thrust; 3 = marked resistance to passive flexion at knee, with boardlike spasticity as result of extension-flexion thrust that yields little to downward pressure below the knee; and 4 = marked resistance to passive flexion at knee with boardlike spasticity as result of extension-flexion thrust that does not yield to downward pressure below the knee.

The third physician is concerned with the administration of various stimuli to induce spasm and the interpretation of polygraph data. The chief technician is charged with operation of the polygraph equipment, with placement of electrodes, and with assisting the third physician in administering stimuli to induce spasm.

Test subjects are oriented regarding the over-all project, including double-blind methodology, and are given 3 weekly polygraph tests before taking the muscle relaxant being studied. Two weeks are then spent in building up to the therapeutic maintenance level as well as in evaluating individual tolerance to the test drug before the start of the double-blind period. Test subjects visit the clinic twice a week up to the time of initiating the double-blind study, then every other week during the double-blind phase, which usually lasts 8 weeks, and for 2 test periods following it. One day is reserved for chemical laboratory work and patient conferences with physicians; the second day is devoted to the polygraph test and to an interview by a designated physician, who also prescribes medication.

The polygraph used in these studies is built around the Offner D Electroencephalograph. The basic instrument was designed as the Harvard Polygraph at the Massachusetts Mental Health Center, Boston, Mass. The polygraph includes coupling units for respiration, ECG, cardiotachometer, raw muscle, and muscle integration. Muscle tension is transmitted by surface electrodes to the muscle integrator, whence it is summated and recorded in these studies as an increase in amplitude of the regularly emitted integrator signal, as demonstrated later in this presentation. From his position the chief technician may view the test subject in an adjacent room through a 1-way mirror. The patient is first observed while a record is taken of him resting on a lounge alone in the examining room. The external stimuli given are of 3 types.

The first method is galvanic stimulation, using a Burdick M-2 stimulator with milliamperage ranging from 0.5 to 60. The stimulating electrode is applied alternately to the left and right quadriceps at the motor point. Stimuli are given upon flashlight signal from the chief technician through the 1-way mirror. This procedure ensures adequate time for a return of the muscle to the resting level before successive graded stimuli are given. The quadriceps muscles are usually selected for stimulation because most of our patients have extensor spasticity of the lower extremities. The second method applies proprioceptive stimulation by subjecting the limbs suddenly to the effect of gravity. This is accomplished by tilting a Barca-lounge, thereby bringing the test subject to a sitting position. A third form of stimulation is carried out by evoking the Babinski sign.

While the patient is still in the laboratory examining room the clinical evaluation of spasticity is performed. Before leaving the Neurological Research Area the patient is interviewed, and medication is prescribed. After a 2-week evaluation of drug tolerance preceding the double-blind period, only the name of the patient, the number of the test, and code label of the drug are put on the prescription blank. The placebo or the active drug is then dispensed at the discretion of the chief of pharmacy, who alone has the key to the code. The placebo and the active drug are identical in appearance and are taken in equal quantities.

Our major efforts with the above polygraph techniques have been the study of 2 drugs: (1) methoxydone (AHR-233*—see FIGURE 1), and (2) carisoprodol (Soma†—see FIGURE 2). To date carisoprodol and methoxydone have not been studied on the same number of patients, nor have they been used for the same period of time; consequently, it is not the design of this paper to present an over-all comparison of the neurospasmolytic effects of these 2 agents.

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* Supplied by A. H. Robins Company, Richmond, Va.

† Supplied by Wallace Laboratories, New Brunswick, N.J.

The results obtained using the described technique after administering methoxydone and carisoprodol to one patient, in separate periods of study, are presented to illustrate the method. The patient, D.C., is a 48-year-old white male with advanced multiple sclerosis, confined to a wheel chair, and having spastic paraplegia with intermittent spontaneous extensor and flexor spasms.

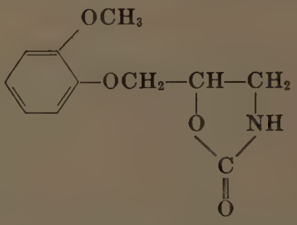

FIGURE 1. Schematic diagram of the molecular structure of methoxydone (5-aryloxymethyl-2-oxazolidinone).

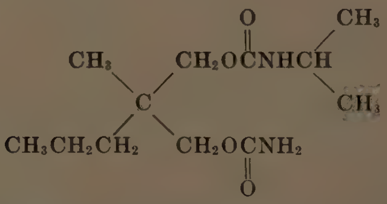

FIGURE 2. Schematic diagram of the molecular structure of carisoprodol: *N*-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate Soma.

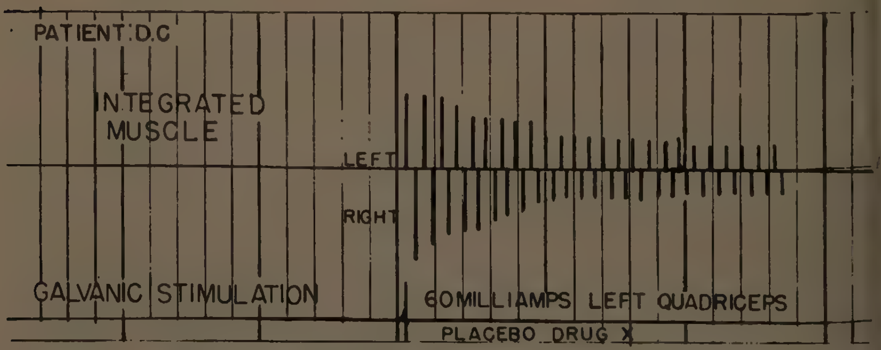

FIGURE 3. Strip of polygraph record illustrating response to 60-mAmp. galvanic stimulus applied to left quadriceps in patient D.C., taking placebo drug X.

The maintenance dose of methoxydone was 4800 mg./day; of carisoprodol, 1400 mg./day.

A few samples of the raw polygraph record illustrate the spasm evoked by galvanic stimulation (FIGURE 3). The test drug has been labeled X. Note the degree of response to a 60-mAmp galvanic stimulus while taking placebo. Note how much less the response is with drug X, demonstrating inhibition of spasticity by drug X (FIGURE 4).

Rather than include our series of prepared polygraph strips demonstrating the effect of the 2 drugs under discussion, for purposes of better visualization a schematic representation of the various polygraph findings is presented.

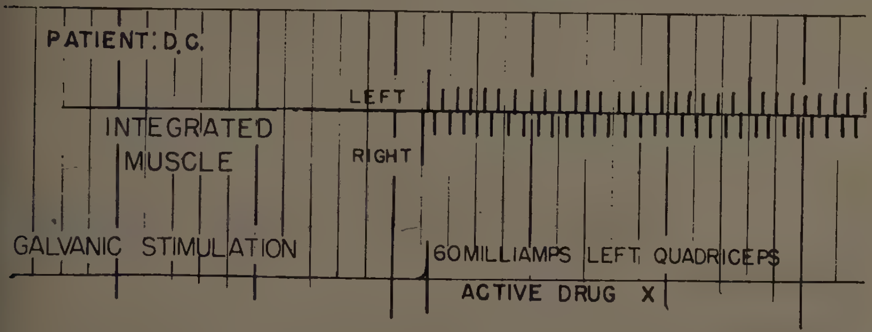

FIGURE 4. Strip of polygraph record illustrating the response to 60-mAmp. galvanic imulus applied to left quadriceps in patient D.C., taking active drug X.

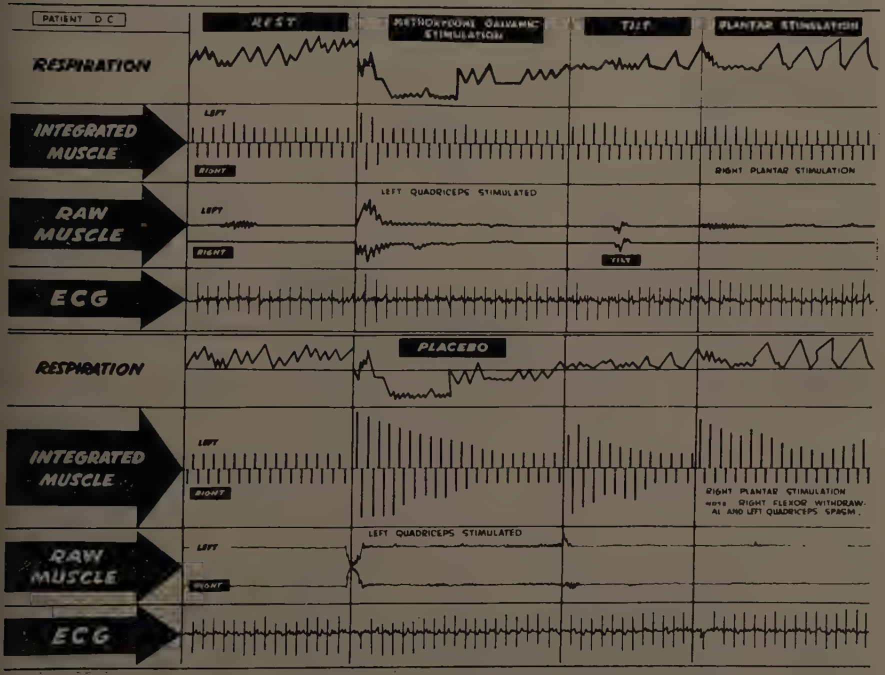

FIGURE 5. Schematic representation of polygraph findings in patient D.C., taking methoxydone.

These have been taken directly from the polygraph records (FIGURE 5). The cardiorespiratory status of patient D.C. is seen to be unaffected by either methoxydone or carisoprodol. Note the integrated muscle responses, especially the differences during stimulation when our patient was taking the placebo, and then compare these responses with those obtained when he was taking methoxydone. It will be seen clearly that the amplitude of our integrated muscle pips during a spasm, plus the duration of the spasm, which together are used to compute the spasm area, are obviously greater during the placebo period than while taking methoxydone. Successive muscle pips form trapezoids with the base line. This has been the basis for the following formula for spasm area:

$$A = \tfrac{3}{2}[(b_1 + b_N) + 2\Sigma\,(b_2 \ldots b_{N-1})]$$

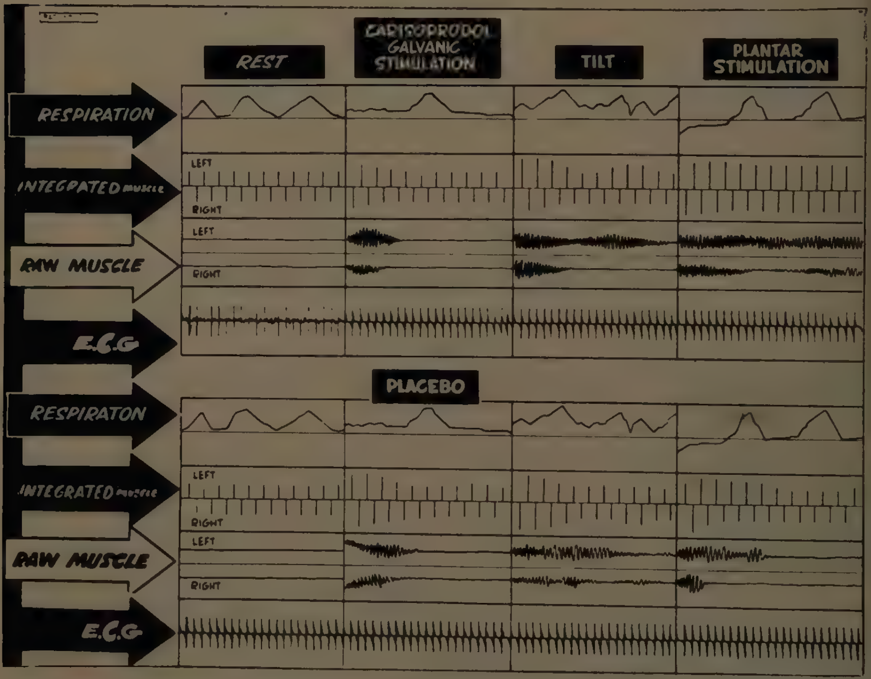

FIGURE 6. Schematic representation of polygraph findings in patient D.C., taking carisoprodol.

In this formula b_1 = first base, b_N = last base, and $(b_2 \ldots b_{N-1})$ = all other bases.

FIGURE 6 represents schematically the responses obtained from stimulation during another double-blind period of study, first when the patient was taking a placebo and then when he was on carisoprodol. Note that with tilt and with plantar stimulation somewhat less spasm is evoked with the placebo than with carisoprodol. However, during galvanic stimulation it is quite clear that more spasm occurs while taking placebo.

A graphic picture of the averages of responses obtained during the double-blind period and plotted as area of spasm in square millimeters is shown in FIGURE 7. In the case of methoxydone it will be noted that, within the various parameters of stimulation, as well as during rest, considerably more spasm area occurs while the patient is on placebo than while he is taking methoxydone. Our most striking picture results with galvanic stimulation, the particular phase during which we exercise our greatest control of the stimulus and obtain the most objective evaluation of response. Here it will be seen that the amount of spasm with methoxydone occupies approximately one fourth the area noted with placebo. In other words, this effect may be interpreted as meaning that methoxydone exercised a 75 per cent inhibition of spasticity during galvanic stimulation.

The results with carisoprodol present a somewhat different picture (FIGURE 8). The averages of the spasm areas during the placebo period were actually a little less than while the patient was taking carisoprodol, except for galvanic stimulation, when the spasm area was obviously higher with placebo. Again, in what we consider the best of our objective tests, we find approximately 45 per cent inhibition of spasticity during galvanic stimulation with carisoprodol.

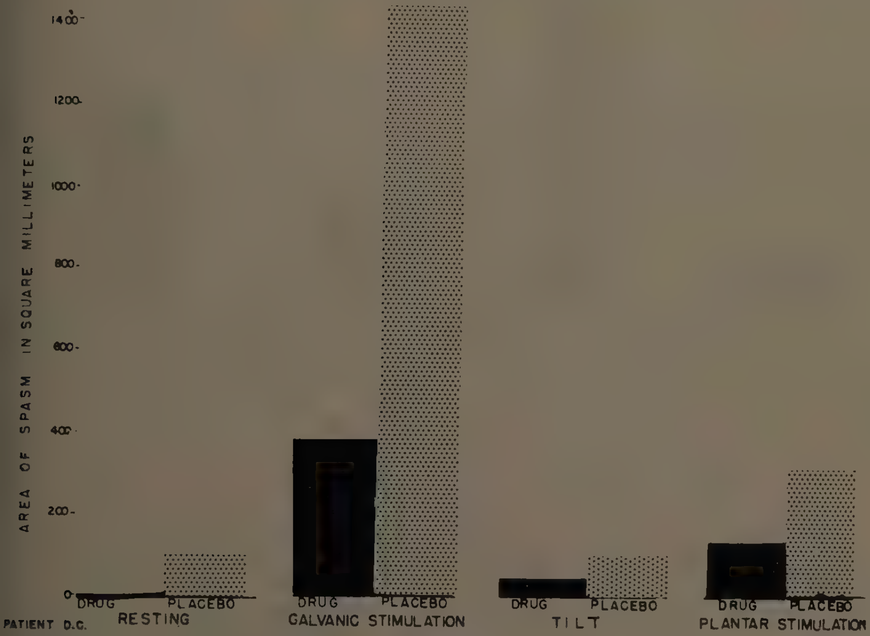

FIGURE 7. Bar graph of spasm areas during the double-blind period with methoxydone (patient D.C.).

Consolidating the averages of all the responses to the various stimuli during the double-blind period and placing the results of methoxydone and carisoprodol on a single graph, we see considerable difference between carisoprodol and placebo effects (FIGURE 9). It may therefore be stated that, under the conditions of testing, in neurospastic disease of patient D.C. methoxydone is a more potent neurospasmolytic agent than is carisoprodol. It remains to be seen whether this will hold true when more patients have been studied and when these drugs have been tested in other disorders associated with an increase of

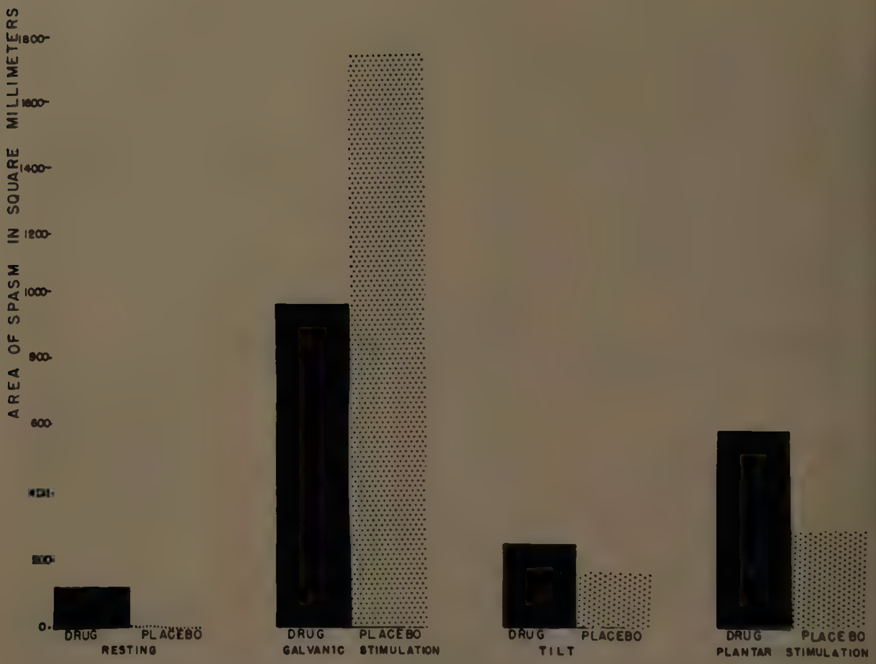

FIGURE 8. Bar graph of spasm areas during the double-blind period with carisoprodol (patient D.C.).

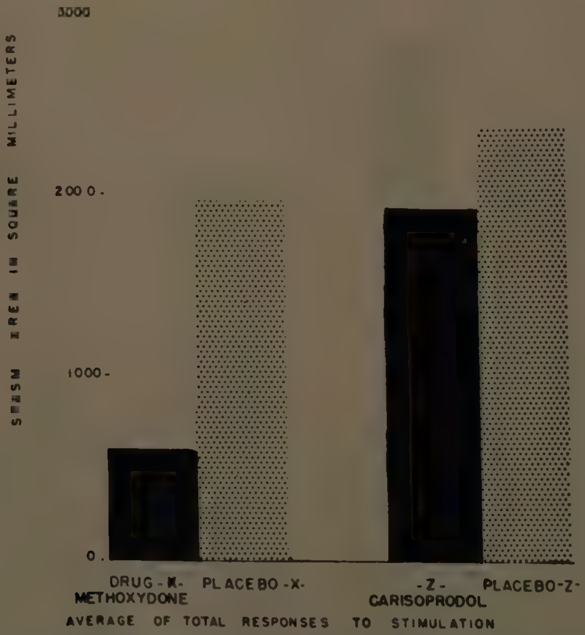

FIGURE 9. Composite bar graph of the spasm areas with methoxydone and carisoprodol during double-blind period (patient D.C.).

muscle tone. A careful survey of the chemical laboratory status with both drugs revealed no particular deviations of hematology, urine, or blood chemistry.

To date the effects of these drugs on 16 patients have been evaluated with the double-blind method and described polygraph techniques totaling about 160 separate polygraph tests. In addition, other muscle relaxants have been subjected to short-term study utilizing polygraph recording techniques. Methocarbamol (Robaxin), given intravenously, has been found to be effective in reducing acute spasms associated with musculoskeletal disorders and disk syndromes. SKF-1572 has been found to be a highly potent neurospasmolytic agent.

Summary

An objective approach to the quantitative assessment of neurospasmolytic agents in man is presented. This is accomplished by administering the test drug under double-blind control and observing its effect through polygraph recording of spasticity obtained as spontaneous spasms at rest and as responses to various stimuli. The stimuli used in these studies are galvanic stimulation, proprioceptive stimulation by tilt, and plantar stimulation. The polygraph records obtained with the patient presented showed that both methoxydone and carisoprodol have neurospasmolytic effect. This method has withstood the tests of reliability and validity through repeat performances and offers a scientific means of quantitatively comparing the effectiveness of different neurospasmolytic agents in man.

EVALUATION OF NONNARCOTIC CHEMICAL AGENTS IN HEADACHES

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Accurate evaluation of drugs used in the treatment of headache presents a twofold problem. Since headache is a symptom, the response to a drug is subjective and evident only to the individual with the headache. Furthermore, the accelerated rate at which new drugs are being evolved makes it difficult for the physician to evaluate critically their therapeutic efficacy.

The present study is based on our observations over the past ten years on the effect of nonnarcotic chemical agents in the treatment of chronic headache. In order to be concise and informative, I shall begin by considering only the three common types of chronic headaches: vascular (migraine), muscular (tension), and posttraumatic. The treatment of other and less common headaches, those associated with hypertension and nasal or paranasal disorders, also will be appraised. In reviewing the results obtained with the various drugs used in the treatment of headache, I have not reported on all of the compounds studied, but have selected only the most effective drugs. A clinical evaluation of the effectiveness of these compounds alone or in combination has been compiled from more than 2500 patients with tension headache and from more than 2500 patients with migraine headache.[1-5] Further appraisal of these drugs and of new drugs not yet reported is being made, using the double-blind technique, standardization of order, and other clinical methods.

Method of Drug Evaluation

Evaluation of the results of treatment with drugs in patients with headache is made on two bases, subjective and objective. Subjective results of the administration of a medicament are determined from the report of the patient, the use of the double-blind technique including the placebo, the use of a standard reference for comparison, standardization of order, correlated data, mathematical validation of differences, and appraisal of side effects. Objectively, some help can be obtained from pulse-wave tracings, electromyography, and pharmacological studies to compare the blood levels of chemical agents with the clinical results. In all studies discrimination among drugs for the relief of pain can be made only by subjects who have pain on which the chemical action can be tested. Between one and two years of study are needed to obtain reliable information as to the effectiveness of a new drug in the treatment of headache.

Treatment of headache by pharmacological agents is often thought of as accomplished by the use of analgesics. In fact, headaches are more frequently treated by other chemical agents, for example, sedatives, tranquilizers, and muscle relaxants for tension and posttraumatic headaches; vasoconstrictors such as ergotamine tartrate in migraine; decongestants for headaches associated with disturbances of the nose and paranasal structures; and antihistaminics for headaches associated with allergy. TABLE 1 lists the factors that influence the results of treatment of headache by pharmacological agents.

The importance of selection of proper medication is shown in TABLE 2.

Clinical use of pharmacotherapy. Headache therapy falls into two categories: (1) symptomatic, or treatment of the individual attack of headache and (2) prophylactic, designed to prevent or reduce the frequency and severity of recurrences. The goals in pharmacotherapy are to interrupt the mechanism producing pain, to raise the pain threshold, and to reduce emotional tension and anxiety responsible for or associated with the pain. The following report is a composite series of some of the drugs and drug combinations with which I have had experience in the treatment of chronic headaches. It must always be remembered that the reaction to pain, as well as the original sensation of pain, is being evaluated. This fact may explain the effectiveness, in pain, of placebos, which are therapeutically inert and cannot be expected to affect the original sensation of pain, but can produce an amelioration of the symptoms by causing a change in the patient's reaction.

TABLE 1

FACTORS INFLUENCING RESULTS OF TREATMENT OF HEADACHE

Pharmacological:
- (1) Selection of proper medication
- (2) Mode of administration
  - (A) Route
    - (a) Oral
    - (b) Rectal
    - (c) Parenteral
  - (B) Timing
- (3) Dosage
- (4) Tolerance

Psychological:
- (1) Personality of patient
- (2) Patient-physician relationship
- (3) Symbolism of medication to patient
- (4) Environmental factors

TABLE 2

Medication	Percentage improved	
	Migraine	Tension
Ergotamine plus caffeine	80	45
Analgesic plus caffeine plus sedative	40	70

RESULTS OF PHARMACOTHERAPY IN SPECIFIC HEADACHE ENTITIES

Tension Headache

Sustained contraction of the skeletal muscles about the head and neck results in pain in the neck and scalp. The most common headache of this type is referred to as tension headache. Such headaches most frequently arise in tense, anxious people whose emotional attitudes are reflected in prolonged and sustained contraction in the nuchal and scalp region. Tension headache may also be a secondary reaction to any other type of headache or disorder in the head and neck including migraine, hypertensive headache, degenerative and neoplastic diseases about the face, head, neck, and cervical vertebrae.

Mechanism. The cause of pain in tension headache is prolonged, excessive contraction of muscles of the head and neck. These vigorous contractions can be demonstrated by action potentials recorded from the muscles of the head and neck.[6] Ischemia that develops in the area of the contracted muscles may play a role in maintaining the pain. Another possible factor responsible for the head pain is the central spread of the excitatory effect of noxious stimulation of the soft tissues of the neck. This spread of pain is carried by the upper cervical nerves and may produce painful sensations in the forehead and face.

Symptomatic treatment. In the treatment of an acute attack of severe or persistent tension headache, the use of nonaddicting analgesics alone is seldom efficient. As ordinarily used, the tranquilizers and sedatives cannot control the discomfort of severe or persistent headaches. In combination, they affect not only the pain threshold, but also the reaction to pain (TABLES 3 and 4). They are particularly effective in the symptomatic treatment of headaches due to tension and of chronic posttraumatic headaches. Our experience indicates that the response to medication obtained with these two types of headache was quite similar. A combination of an analgesic, sedative, and/or tranquilizer gives effective relief in 71 per cent of treated cases, whereas analgesics or sedatives when used alone are less effective (62 per cent).

TABLE 3
TENSION HEADACHE
Symptomatic Treatment of 500 Patients

Medication	Action	Percentage improved
Acetylsalicylic acid	Analgesic	55
Dextropropoxyphene hydrochloride (Darvon)	Analgesic	62*
Amobarbital sodium (Amytal)	Sedative	50+
Placebo		45 ± 5

* Evaluation not completed.

Prophylactic treatment. Prophylactic treatment of tension headaches by pharmacological agents has changed in recent years because of the introduction of tranquilizers and central muscle relaxants. Tranquilizing drugs are effective in controlling tension headaches and the associated autonomic nervous system signs in some patients (65 per cent); in others with similar symptomatology they are not effective. TABLE 5 summarizes some of our experience with the use of tranquilizers in prophylactic treatment of these patients.

In our previous experience the use of skeletal muscle relaxants in preventive treatment of tension headache has not been successful. However, preliminary evaluation of a new muscle relaxant with analgesic properties, carisoprodol (Soma), has been found to be an effective adjunct in the management of tension headaches (67 per cent; *see* TABLE 6). Further investigation of this and other similar compounds is in process. In TABLE 6 attention is called to our results with carisoprodol and other compounds in the treatment of tension headaches. Objective evidence of the action of carisoprodol can be observed in the electromyograph (EMG) tracings shown in FIGURES 1 and 2.

TABLE 4
TENSION HEADACHE
Symptomatic Treatment of 1500 Patients

Medication	Action	Percentage improved
Aspirin Phenacetin Caffeine Sandoptal (Fiorinal)	Analgesic Analgesic Stimulant Sedative	71
Dextropropoxyphene hydrochloride (Darvon) Aspirin Phenaglycodol	Analgesic Analgesic Tranquilizer	71*
Aspirin Perphenazine (Trilafon) Orphenazine hydrochloride (Disipal) Caffeine (Tenjen)	Analgesic Tranquilizer Muscle relaxant Stimulant	65*
Placebo		45 ± 5

* Evaluation not completed.

TABLE 5
TENSION HEADACHE
Prophylactic Treatment of 1250 Patients

Medication	Action	Percentage improved
Meprobamate (Miltown; Equanil)	Tranquilizer	65*
Phenaglycodol (Ultran)	Tranquilizer	58
Reserpine (Serpasil)	Tranquilizer	54
Chlorpromazine HCl (Thorazine)	Tranquilizer	52
Placebo		45 ± 5

* Evaluation not completed.

Migraine (Vascular) Headache

This condition is a symptom complex consisting of periodic, unilateral, recurrent headache, often associated with nausea and vomiting and preceded by a variety of prodromal symptoms, including visual disturbances. Frequently a history of similar headache in the parents or other members of the family is noted. Although headache is the most prominent feature of migraine, the syndrome may manifest itself in widespread derangement of bodily function.

The painful phase of migraine is associated with vasodilatation, during which the cranial vessels have altered sensitivity and increased amplitude of pulsation. The arteries usually involved are extracranial, and their record of pulsation shows a very high amplitude. Recent studies indicate that the

TABLE 6
TENSION HEADACHE
Prophylactic Treatment of 750 Patients

Medication	Action	Percentage improved
Meprobamate (Miltown)	Tranquilizer	65*
Carisoprodol (Soma)	Muscle relaxant	67*
Bellafoline† Phenobarbital (Belladenal)	Antispasmodic Sedative	60
Amobarbital sodium (Amytal)	Sedative	55
Placebo		45 ± 5

* Evaluation not completed.
† A natural levorotatory alkaloid of belladonna.

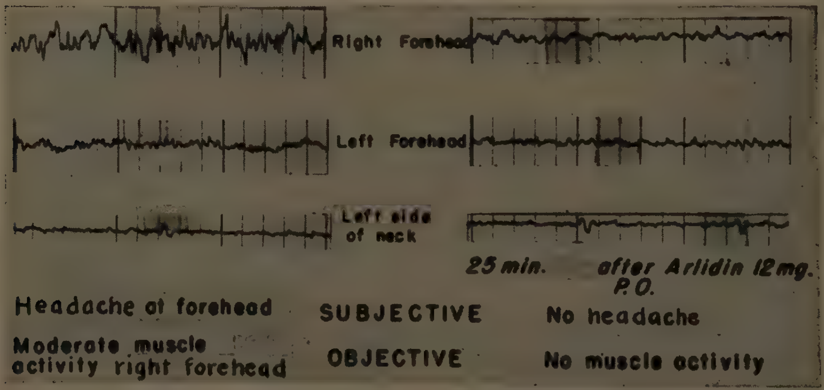

FIGURE 1. Electromyograph (EMG) tracing of tension headache (patient H.K.) before and after the oral administration of Arlidin hydrochloride (phenyl-2-butyl-norsuprifin HCl), a deep muscle peripheral vasodilator.

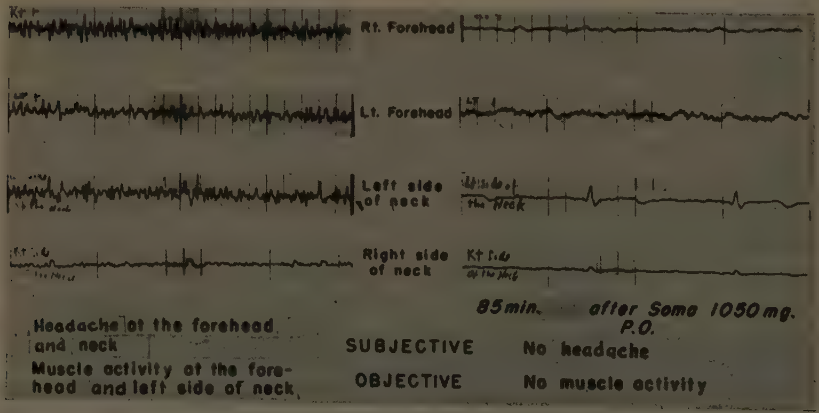
Rt. Forehead
Lt. Forehead
Left side of neck
Right side of neck
85 min. after Soma 1050 mg. P.O.
Headache at the forehead and neck
SUBJECTIVE
No headache
Muscle activity at the forehead and left side of neck
OBJECTIVE
No muscle activity

FIGURE 2. EMG tracing of tension headache (patient H.K.) before and after the oral administration of Soma (carisoprodol), an analgesic.

sensitivity of the blood vessels is in part due to local vascular changes, particularly in the arterial capillaries, which result in accumulation of a substance of low molecular weight (bradykinin), which may be responsible for lowering the pain threshold.[7] The presence of this substance apparently renders the distention of large arteries painful, so that the headache ultimately results from a combination of altered sensitivity of the vessel plus vasodilatation.

Symptomatic treatment. Introduction of the use of ergotamine tartrate in the treatment of acute attacks of migraine is an excellent example of relieving head pain without any direct analgesic effect. The benefit that occurs following administration of this drug is probably due to the direct action of the substance on the smooth muscles of the blood vessels, since it produces a constriction of these vessels and a decrease in amplitude of pulsation. More recently, the antiserotonin activity of ergotamine suggests that other mechanisms play a part in its therapeutic effectiveness. This effectiveness in migraine therapy has been improved further by combining the drug with caffeine to potentiate its action and by combining it with other compounds to reduce its side effects and control some of the symptoms associated with migraine. Objective evidence of response to ergotamine tartrate in a patient with migraine headache is well illustrated in the pulse volume tracing shown in FIGURE 3.

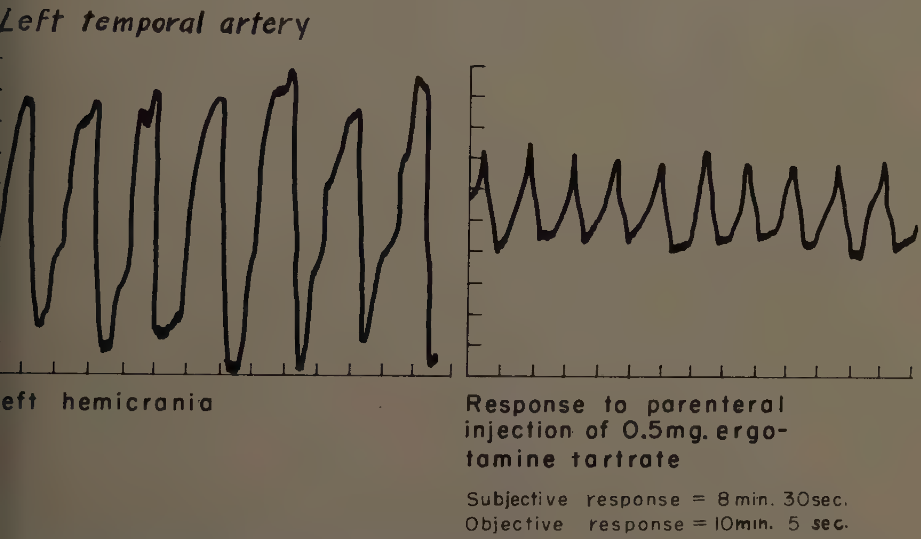

FIGURE 3. Pulse volume tracing, showing response to ergotamine tartrate in a patient with migraine headache.

Some of the various forms in which ergot is available and our results with treatment are indicated in TABLE 7.

Prophylactic treatment. Efforts to prevent chronic vascular headache by the use of drugs have been uniformly unsuccessful, with few exceptions. Therefore, any new drug that may be of value in the prevention of migraine warrants investigation. A previous study on the action of serotonin in migraine patients[8] and the fact that ergotamine tartrate has some antiserotonin action led us to study the effects of a certain antiserotonin antagonist, namely, methyl lysergic acid butanolamide (UML 491) in the prevention of migraine headaches.[9] The following is a preliminary report on our observations with 36 patients who were treated for from 1 to 2 months with UML 491. Patients in this group were selective in that they did not respond satisfactorily to the forms of medical or psychiatric treatment commonly used in such cases; symptoms were severe and tenacious. The results are summarized in TABLE 8.

TABLE 7
MIGRAINE HEADACHE
Symptomatic Treatment of 2500 Patients

Medication	Action	Percentage improved
Ergotamine tartrate Caffeine (Cafergot)	Vasoconstriction	80
Ergotamine tartrate Caffeine Pentobarbital sodium Bellafoline Mercaptothiazinyl (GFPS 71)	Vasoconstriction Sedation Antispasmodic Antiemetic	88*
Ergotamine tartrate Caffeine Cyclizine hydrochloride (Migral)	Vasoconstriction Antiemetic	75*
Medihaler (ergotamine)	Vasoconstriction	70*
Placebo		25

* Evaluation not completed.

TABLE 8
MIGRAINE HEADACHE
Prophylactic Treatment of 40 Patients

Medication	Action	Percentage response		
		Excellent	Good	Poor
Methyl lysergic acid butanolamide (UML 491)	Serotonin antagonist	45	40	15

Optimism mixed with caution regarding the effectiveness of UML 491 in the treatment of vascular headaches is all that can be offered at this time. However, further investigation with UML 491 and other antiserotonin compounds is being carried out, and these drugs may prove to be an important adjunct in the management of vascular headache. In the interim treatment of vascular headache we are also studying certain monoamine oxidase inhibitors such as phenelzine (Nardil) which, in certain instances, have proved surprisingly effective.

Headaches Associated with Hypertension

At one time or another, severe headache is a major complaint of most patients with essential hypertension. The pathogenesis of headache in essential hypertension is somewhat obscure. The degree of headache does not correlate well with the blood-pressure level; the headache may be present when the blood pressure is low as well as when it is high. It is postulated that variations in the contractile state of the cranial arteries are the cause of the pain, and that the elevated blood pressure is only an accessory factor. After the administration of ergotamine tartrate the headache usually disappears, which would indicate that the mechanism may be similar to that of migraine. Another variety of headache occurring with hypertension is a suboccipital tightness and rigidity that may encircle the head. This pain is due to muscle spasm and is similar in mechanism to tension headache.

Treatment of hypertensive headache. In the treatment of this condition, management of the general state of hypertension is always indicated, aiming at a decrease in the blood pressure and protection of the patient against vascular insults. The measures available for lowering the pressure include psychotherapy, rest, sodium restriction, specific antihypertensive drugs, and sympathectomy.

TABLE 9
TREATMENT OF HEADACHES WITH RESERPINE

	Percentage improved
Hypertension	77
Tension	54
Migraine	38
Placebo	50

The following is a report of our study with a group of hypertensive patients receiving reserpine. These results are compared with those obtained in migraine and tension headache sufferers receiving reserpine (TABLE 9).

It is interesting to note that in all these studies the patients with hypertension responded most favorably, those with tension headache moderately well, and those with migraine the least well. It is also of interest to note that, in those patients with headaches associated with hypertension who obtained no relief from headache, there was a reduction in blood pressure similar to that experienced in patients who reported improvement. However, all of these results must be considered in the light of favorable responses to treatment with placebos, which in previous studies were effective in approximately 50 per cent of observed cases.

Headaches Associated with Disorders of the Nasal and Paranasal Structures

Headache encountered in sinusitis can be due to a variety of factors, including inflammatory changes in mucosa of the ostium of the sinus and engorgement of the turbinate with impingement on the septum. The importance of differential diagnosis in this type of headache in relation to treatment is obvious. The treatment of acute infections of any of the sinuses is directed toward eradication of the infection and improvement of sinus ventilation and drainage. Nasal shrinkage may give great relief to the patient. In the patients with vasomotor (allergic) rhinitis, local treatment supplemented by the use of sympathomimetic amines and antihistaminics may produce effective relief. The following is a preliminary report of symptomatic medical treatment with a combined preparation including an analgesic, an antihistaminic, and a vasoconstrictor (TABLE 10).

Our observations would indicate that this combined preparation is an effective oral medication for symptomatic treatment of vasomotor rhinitis. Further appraisal of the effectiveness of this compound is being done.

TABLE 10
HEADACHES ASSOCIATED WITH DISORDERS OF NASAL AND PARANASAL STRUCTURES

Medication	Action	Percentage improved
N-acetyl-para-aminophenol	Antihistaminic	
Acetophenetidin	Analgesic	
Phenyltoloxamine dihydrogen citrate	Tranquilizer	
Phenylpropanolamine hydrochloride (Sinutab)	Vasoconstrictor	65*
Acetylsalicylic acid	Analgesic	50

* Evaluation not completed.

CONCLUSION

Logical approach to the treatment of headache depends upon understanding the mechanisms involved in its production. The physician must recognize the fact that pain, particularly when related to the head, has two aspects, physiological and psychological. The personal influence of the physician is most important in the effectiveness of the drugs. Good results obtained with many remedies are frequently based on this fact. Treatment of headache is much easier to write about than to put into action. In some patients serious emotional problems and adverse environmental factors make admission to a hospital necessary to clarify both the physiological and the psychological aspects of the problem. However, the majority of patients can be helped if there is a good physician-patient relationship, regular office visits, and a flexible approach to treatment.

In emphasizing the pharmacological aspects of the treatment of headaches, attention must be called to the fact that drugs cannot replace insight and understanding of emotional problems, which are frequently the major cause of chronic headache.

REFERENCES

1. FRIEDMAN, A. P., C. BRENNER & S. CARTER. 1949. Symptomatic treatment of certain types of chronic headache. J. Am. Med. Assoc. **139:** 195.
2. FRIEDMAN, A. P. 1957. Use of tranquilizers in the treatment of headache. Am. Practitioner and Dig. Treatment. **8:** 94.
3. FRIEDMAN, A. P. & H. H. MERRITT. 1957. Treatment of headache. J. Am. Med. Assoc. **163:** 1111.
4. FRIEDMAN, A. P. 1958. Treatment of headache. Med. Clin. N. Am. **42:** 659.
5. FRIEDMAN, A. P. & H. H. MERRITT. 1959. Headache: Diagnosis and Treatment. Davis. Philadelphia, Pa.

6. Tunis, M. M. & H. G. Wolff. 1954. Studies on headache: cranial artery vasoconstriction and muscle contraction headache. A. M. A. Arch. Neurol. Psychiat. **71:** 425.
7. Ostfeld, A. M., L. F. Chapman, H. Goodell & H. G. Wolff. 1956. Studies in headache: a summary of evidence implicating a locally active chemical agent in migraine. Trans. Am. Neurol. Assoc. 81st Meeting. **:** 356.
8. Kimball, R. W., A. P. Friedman & E. Vallejo. 1960. Effect of serotonin in migraine patients. Presented at Am. Acad. Neurol. Meeting. J. Neurol. **10:** 107.
9. Friedman, A. P. Clinical observations with methyl-lysergic acid butanolamide tartrate in vascular headache. Angiology. To be published.

THE ROLE OF CARISOPRODOL IN PHYSICAL MEDICINE

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The objectives of physical medicine are to relieve pain, to improve tissue metabolism, and to enhance the ability of the patient to perform significant movements. The achievement of these objectives depends on many factors in addition to the actual physical effects of energy applied or physiological responses elicited by physical procedures. Any means by which clinical improvement may be enhanced is a proper objective of study in medicine. In a search for such means, carisoprodol (*N*-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate) was chosen for a clinical study in relation to physical medicine by reason of properties that, on the basis of preliminary studies, seemed to offer possible improvement in the results of physical treatment. Physical therapy is related specifically to the stretching of muscles, tendons, and ligaments, to the mobilization of joints and, particularly, to exercise.

Muscle strains result from sudden application of a stretching force, the degree of strain varying with the force applied. The resultant pathological state in muscle will exhibit a variable amount of edema, and, often hemorrhage, induration, and muscle spasm. Circulatory disturbance, relative hypoxia, and pain occur, followed by fibrosis. Sprains of ligaments exhibit similar changes expressed as fixation of the parts, muscle spasm, pain, and induration. Inflammatory conditions in muscle, fascia, or joints tend to cause spasm along with all the adverse effects of trauma, as well as infiltration, degeneration, ischemia, or even necrosis. Physiological responses that are necessary initially for protection against further damage often prolong the period of immobilization and ischemia of soft tissues. The resultant fibrosis is notoriously apt to lead to permanent impairment, adaptive shortening, and disability.

The usual sequence of essential measures prescribed to counteract the adverse histologic and metabolic changes of trauma and inflammation includes heat in some effective form, mobilization, and stretching of contractile and elastic elements of the affected part, all leading to movement and active exercise. Movement is essential to the restoration of function of the movable parts of the body and to restoration of the integrity of tissues. It is our strong conviction that significant movement is a major goal of the healing arts.

Repetitive heating has been shown by numerous investigators[1] to increase the vascularity of the tissues. This is demonstrated by an increase in the number of patent blood vessels and in the volume of blood flow. This results in increased local metabolism of the part and in an increased number of histiocytes in the tissues, as I have shown in unpublished studies. Stretching of elastic and contractile tissues tends to restore normal muscle length[2] and hence to improve performance and strength and to restore normal length of ligaments. Increases in mobility and metabolism are accompanied by reduction of pain. It cannot be overemphasized that physical therapy results in microscopic and gross anatomical changes in tissue, especially muscle, fascia, and blood vessels.

Procedure

A group of 84 cases was selected in which muscle spasm, vasospasm or ischemia, and adaptive shortening were characteristic. This group included cases of sprains, strains, contusions, bursitis, tenosynovitis, nerve-root compression or radiculitis, and myositis, fibrositis, and both degenerative and rheumatoid arthritis. Where practicable, the mobility of related parts was measured by protractor at appropriate intervals. Muscle strength was tested by the deLorme[3] or other techniques of muscle grading, and every effort was made to quantify indices of improvement under the clinical conditions of this study. The presence of pain and local tenderness was noted, but these factors were given only accessory weight in determining grades of improvement. The age range was from 24 to 57 years, the median age being 42.2 years.

The patients were treated by the usual physical methods under standard clinical conditions by registered physical therapists, using standard equipment and following the prescription of the physiatrist. Pertinent measurements were taken in the initial examination and repeated at regular intervals during the course of observation. Initially, standard physical therapy was used exclusive of drugs for the first two or three weeks. The medication under investigation was then added, and the single-blind placebo method was used as control. Carisoprodol* was prescribed in a dosage of 350 mg. 4 times daily. The placebo tablets were exactly the same size, shape, and color as the drug tablets. Patients were asked simply to take the tablets as part of their regular medical management. All these patients were refractory cases from a referral practice or a community rehabilitation center.

An attempt was made to determine whether the medication elicited any measurable increment of improvement over that obtained in the initial period of physical treatment. Statements of patients regarding sleep and ability to perform certain routine tasks and to return to employment were correlated with the objective measurements taken. The ratings of the therapists, the medical observers, and the patients were tabulated and weighed against the objective measurements recorded during physical therapy plus drug or placebo. Efforts to assign percentile values to the observed changes will not be reported at this time.

Results

Of the 84 patients, 56 (14 men, 42 women) were studied in sufficient detail to permit a qualitative report of results. Measurable parameters were so varied as to preclude valid statistical evaluation in this preliminary analysis.

Without exception, the 26 patients under treatment for sprains, muscle strains and contusions showed increments of gain upon addition of carisoprodol, as compared with their responses to previous regular physical therapy. The majority of this group, 24 in number, described pain relief, and all showed increased ranges of motion and muscle strength and release of muscle spasm. These changes became apparent in a rather short time—two to three weeks, on the average, after the beginning of the combined therapy—in contrast to the prolonged periods of impairment prior to institution of the combined treatment.

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* Supplied by the Wallace Laboratories, New Brunswick, N.J.

The 7 patients with chronic bursitis, tendinitis, and capsulitis showed similar responses, but increments of gain were less rapid and dramatic, varying from slight to marked, as indicated by increases in range of motion, muscle strength, and ability to do gainful work. These patients returned to work within an average of 4.2 weeks after the start of combined therapy.

The reactions of the 5 patients with rheumatoid arthritis and spondylitis varied according to the degree of activity and the stage of the disease at the time therapy was begun. Four patients showed further reduction of palpable muscle spasm and slight to marked increases in ranges of motion of affected joints. One patient exhibited no changes and experienced no pain relief; it was later discovered that he had been on placebo tablets during the entire course of his treatments. Of the 5 cases of myositis and fibrositis, 2 were markedly better on combined therapy, 1 was moderately improved, and 2 showed no measurable improvement.

Cervical nerve root compression or radiculitis, of which 5 cases are reported, is often associated with trauma or degenerative arthritis and commonly with both. Etiological factors are usually complex. Physical treatment includes depth heating, massage of neck and back muscles, and traction. The effectiveness of such therapy depends to a large degree on the amount of muscle relaxation and mechanical stretching of neck structures that can be achieved, the degree of distraction of skeletal elements, and decompression of nerve roots. Repetition of effective treatments of this type results in tissue readjustments that may be permanent. Increments of gain in neck motion range, reduction or erasure of muscle spasm, and subjective relief of pain were marked in 4 of these patients, and moderate in 1.

In one case of cerebral palsy, a 40-year-old man who had sustained multiple sprains of cervical and lumbar spinal ligaments and severe back muscle strains in an automobile accident, a marked reduction of hyperactive stretch reflexes and ablation of a life-long bilateral ankle clonus was observed as a result of prolonged physical treatment plus carisoprodol. The clonus and exaggerated tendon reflexes reappeared 3 days after drug administration was stopped, but disappeared when it was resumed. Slow improvement in neck and back muscles continued.

Degenerative arthritis associated with painful muscle spasms and tension was the indication studied in 8 cases. The addition of carisoprodol to routine physical therapy resulted in measurable increases in the ranges of motion of involved parts and also provided relief of pain in 4 cases and partial improvement in 2; in 1 case, no improvement occurred.

Adverse side effects were of a minor nature, and in no case in this series were they of such a severe nature as to require discontinuance of the drug. Six of the 56 patients noted a sleepiness sufficient to render a reduction in dosage advisable; with all 6, omission of the midday dose was sufficient to correct for this factor. One patient reported epigastric distress after taking the drug for 6 days; omission of the medication for 3 days relieved the symptoms. Two patients developed hives within 2 days after starting the drug. These disappeared promptly after withdrawal of the medication. The relative lack of side reactions was commented on by the staff members concerned with the series. The influence of the placebo was negligible in the entire series, being indistinguishable from the progression of changes due to physical therapy alone.

Discussion

A significant number of the patients studied showed increments of gain in ranges of motion, elasticity of fasciae and muscle strength, and reduction of palpable muscle spasm and pain after carisoprodol was added to physical therapy. This conclusion is based on clinical judgment, without a formal attempt to apply statistical methods. The results tend to verify the observations of Berger and his co-workers[4] on the relief of pain, produced by injection of silver nitrate into the joints of rats, through administration of carisoprodol in nontoxic doses. The authors interpreted this relief not as an anti-inflammatory effect, but rather as evidence of depression of pain responses in the mid-brain reticular formation or the nucleus lateralis of the diffuse thalamic system.

Muscles that are in constant tension or spasm have been shown by Dickel and his associates[5] to require the extra energy supplied by adenosine triphosphate in order to relax. Both heat and carisoprodol have been shown to enhance muscle relaxation.[1,4] One may postulate some restoration of the energy store of muscle by the additive effects of these two factors, as evidenced by observed improvements in passive stretch, muscle strength, and pain relief in spastic muscles. The increases in ranges of joint motion may be corollary to this cumulative effect of physical and pharmaceutical factors, through restoration of a more nearly normal muscle metabolism. The restoration of increased blood volume flow and oxygen exchange incident to this improvement in metabolic gradient in muscle is accompanied by a parallel improvement in that of all associated tissues. Hence the observed tendency toward resolution of exudates, reduction of infiltrates, and fibrosis.

Much physical medicine is directed toward alteration of the physiological state of neuromuscular receptors, expecially those of the muscle spindles. Fischer and Solomon[6] state that the stationary frequency of the muscle spindle discharges evoked by a given tension varies slightly with the absolute temperature of the spindles, and that a quick warming of the spindles causes a temporary but complete inhibition of the firing of the spindles, whereas sudden cooling elicits a short burst of excitations. The demonstrated effects of a variety of meprobamate derivatives and other muscle-relaxant drugs would tend, in theory, to potentiate the known effects of heat, stretching, massage, and exercise on the neuromuscular spindles, with their small fiber feedback system which modulates muscle action. A reduction of proprioceptive (muscle) stimuli, plus an inhibition of pain responses in the diencephalon, would certainly tend to break the vicious circle of tense muscles, tied-up energy, pain, ischemia, and anxiety such as we commonly see in many patients who have suffered pain in some segment of the body for any length of time.

We may conclude that carisoprodol does exhibit measurable potentiating effects on certain responses to physical procedures in the treatment of a variety of traumatic and inflammatory neuromuscular conditions.

References

1. Krusen, F. H. 1941. Physical Medicine. : 59–69. Saunders. Philadelphia, Pa.
2. Darling, R. C. 1958. Physiology of exercise and fatigue. *In* Therapeutic Exercise. : 30–31. S. Licht, Ed. Licht. New Haven, Conn.
3. DeLorme, T. L. & A. Watkins. 1951. Progressive Resistance Exercise. Appleton-Century-Crofts. New York, N.Y.
4. Berger, F. M., M. Kletzkin, B. J. Ludwig, S. Margolin & L. S. Powell. 1959. Unusual muscle relaxant and analgesic properties of N-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate (carisoprodol). J. Pharmacol. Exptl. Therap. **127**: 66.
5. Dickel, H. A., J. A. Wood & H. H. Dixon. 1957. Electromyographic studies on meprobamate and the working, anxious patient. Ann. N. Y. Acad. Sci. **67**(10): 780–788.
6. Fischer, E. & S. Solomon. 1958. Physiological responses to heat and cold. *In* Therapeutic Heat. : 146–147. S. Licht, Ed. Licht. New Haven, Conn.

CLINICAL EVALUATION OF CARISOPRODOL IN CEREBRAL PALSY

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A review of the literature on carisoprodol indicates satisfactory results with regard to muscle relaxation and analgesia.[1-3] The only untoward reactions noted in these reports were drowsiness and in rare instances the occurrence of a rash.

To date, the exact mode of action of drugs such as carisoprodol has been rather confusingly and vaguely defined. Concurrently with a vast number of so-called tranquilizers that have been flooding the field, we have references to internuncial blocking agents, acetylcholine neutralizers, and amine oxidase inhibitors. On the whole, the exact nature of the reactions involved, in my opinion, has been difficult to understand and appreciate.

From a clinical standpoint, there are many factors in favor of the theory of Spears and Phelps[2] that carisoprodol produces a kinesthetic block in the cerebellum. Much work needs to be done before definite proof of this theory is obtained. Other mechanisms may be what might be called inhibition of excessive facilitation and facilitation of decreased inhibition. Either of these actions could take place in the reticular system of the brain stem.

In two cases, children who were receiving 350 mg. carisoprodol twice daily developed tremor within a few days. In one instance the parents refused to continue the drug. In the other case, the tremor disappeared when the dose was increased to 700 mg. twice daily. Both of these children were athetoids with compensatory muscle spasm. The observed tremor may result from drug action of the following types: stimulation of the activating areas, sufficient stimulation to release a tremor, or sufficient relaxation of the spastic muscle to permit the rhythmic contractions of the antagonistic muscles.

Two of the children had Jacksonian convulsions during the period of drug administration. One had rigidity and the other spasticity; both patients were topographically quadriplegic. We did not attribute these convulsions to the action of carisoprodol because they existed before the onset of this treatment. In one instance, phenobarbital administration had been discontinued because of a possible conflict with carisoprodol; the convulsions stopped when phenobarbital was resumed. Furthermore, no other children developed convulsive attacks.

It was decided that improvement could be measured in terms of degrees of relaxation of the muscles involved. Increases in the range of passive movement could be gauged with the protractor or by the patient's ability to lock the braces. In addition to this, the patient's over-all response to therapy could also be of value.

A 250-mg. capsule, and later a 350-mg. capsule, of carisoprodol was administered twice daily. The dose was then increased to 700 mg. twice daily and in one instance 1050 mg. was given three times a day with no untoward results. It was decided to give all new cases initial doses of 700 mg. twice daily. In a few instances where the child was unable to swallow the tablet, the 250-mg. capsule was emptied into the child's cereal, and no rebellious reaction was evident.

Results

In four instances, no benefit was noted. One child, who had a posterior and upward dislocation of one hip joint due to improper shelving of the acetabular ridge and who was suffering considerably, did not appear to respond to this drug. Two others (those mentioned above) had inadequately controlled convulsive seizures; the fourth was the child who developed tremors, following which the mother discontinued medication. A child with a high intelligence quotient developed more stiffness in his arm. He had hemiathetosis, and his principal problem seemed to be a rejection of the involved arm. At present he is under psychiatric care. One child did not improve from the standpoint of locomotion, but the speech therapist reported that his speech had improved more during this drug therapy than it had in the previous two years. We found improvement in speech in several other instances.

In all the remaining cases, therapists noted improvement in gait and increased comfort and ease of motion in patients wearing braces.

This report comprises the evaluation of the results of administration of carisoprodol to twenty-two children, the most severely handicapped of a group of more than five hundred children under our care and, in addition, some who had particular problems such as convulsive seizures and psychiatric manifestations. Relaxation was accomplished in a vast majority of instances, most notably in the less handicapped children.

The exact mode and location of action of carisoprodol do not seem to have been established definitely. In our opinion, the drug neither increases nor decreases the tendency toward convulsive seizures. As demonstrated in one instance, it did not produce sufficient tranquilization to affect motor activity in a child with a psychiatric problem. Drowsiness as a side effect seems to be insignificant and of short duration.

We do not believe that carisoprodol is the complete answer to the problem. Our observations indicate, however, that it is a distinct advance toward the solution of it. It does not eliminate bracing or therapy, but it does enhance reactions to therapy. In summary, carisoprodol is the most satisfactory muscle relaxant we have found thus far, and its untoward effects are negligible.

References

1. Spears, C. E. 1959. The clinical evaluation of carisoprodol in cerebral palsy. *In* The Pharmacology and Clinical Usefulness of Carisoprodol. : 138–143. J. Miller, Ed. Wayne State Univ. Press. Detroit, Mich.
2. Spears, C. E. & W. M. Phelps. 1959. Arch. Pediatrics. **76:** 287–292.
3. Miller, J. 1959. Pharmacology and Clinical Usefulness of Carisoprodol. Wayne State Univ. Press. Detroit, Mich.

THE EFFECT OF CARISOPRODOL IN GENERAL POSTOPERATIVE SURGERY

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Carisoprodol is reported to have analgesic properties, without serious side effects, in a number of clinical syndromes, suggesting the possibility of an effective postoperative medication. In consequence we designed a clinical study to evaluate the drug in the postoperative care of the surgical patient.

Procedure. A preliminary study was carried out on about 50 patients, using increasing doses of carisoprodol, until an oral dosage was reached that was believed to be giving significant relief of pain. This dosage was 1400 mg., which is 4 times the usual recommended dose. At this dosage level, occasional patients also demonstrated the side effect of severe drowsiness.

On the basis of the preliminary study, we launched a double-blind study using carisoprodol, meperidine, and placebo in identical capsules. The capsules were filled so that each contained respectively 350 mg. carisoprodol, 25 mg. merperidine, or placebo, which was 99 per cent lactose and 1 per cent magnesium stearate. The orders were so written that the capsules replaced parenteral medication as soon as the patient was able to take fluids orally. The 3 kinds of capsules were dispensed to patients on a completely random basis by the hospital pharmacist, and the drug given was unknown to everyone involved in the care of patients, including the surgeon who scored its pain-relieving effect. By this technique, 45 routine postoperative general surgical patients received 4 capsules at a time, on 1 or more occasions, for the relief of pain. Fifteen of these patients received carisoprodol (1400 mg.), 15 received meperidine (100 mg.), and 15 received placebo.

Each dose was evaluated during the first hour following administration by a single surgeon observer, and 2 scores were recorded. One score was based on the observer's impression of the relief afforded by the medication; the other score was based on the patient's impression of the relief afforded by the medication. A score of 0 represented no relief, 1 represented inadequate relief, 2 represented adequate relief, and 3 represented complete relief. If there was not adequate relief at the end of 1 hour, the unknown capsules were supplemented by a known analgesic medication; if a patient repeatedly did not get adequate relief from his assigned capsules, they were discontinued.

Results. An average score was calculated for the amount of relief of pain given by 4 capsules to each patient. TABLE 1 shows the details concerning operative procedure undertaken, the number of doses of carisoprodol administered, the surgeon's impression of relief of pain, and the patient's impression of relief of pain in the 15 patients studied. TABLE 2 shows analysis of the 15 patients receiving 4 capsules of placebo, and TABLE 3 the same details with respect to the 15 patients receiving meperidine. TABLE 4 summarizes the results of the preceding 3 tables.

The individual patient's average relief scores were averaged to give an average relief score for each of the 3 medications. The average relief score

TABLE 1

CLINICAL EVALUATION OF PAIN RELIEF RESULTING FROM THE ADMINISTRATION OF CARISOPRODOL* IN POSTOPERATIVE SURGERY

Surgical procedure	Number of doses	Average of surgeon's impressions of relief of pain	Average of patient's impressions of relief of pain
(1) Excision of thyroid nodule	2	2.5	2.5
(2) Cholecystectomy and appendectomy	2	3.0	1.5
(3) Lung biopsy and exploratory laparotomy	6	2.3	2.3
(4) Hemorrhoidectomy and subtotal thyroidectomy	3	0.7	0.7
(5) Esophagoscopy and transthoracic repair of diaphragmatic hernia	5	2.0	2.0
(6) Bilateral inguinal hernia repair	3	1.0	1.0
(7) Cholecystectomy and choledochostomy	3	0.0	0.0
(8) Esophagoscopy, subtotal gastrectomy, splenectomy	2	0.0	0.0
(9) Inguinal hernia repair	3	2.3	2.3
(10) Hysterectomy, cystocele, and rectocele repair	3	0.7	0.7
(11) Appendectomy	2	0.5	0.5
(12) Wertheim hysterectomy, appendectomy	2	3.0	3.0
(13) Hysterectomy, appendectomy, excision of cyst of eyelid	3	2.0	2.0
(14) Cholecystectomy, excision of epithelioma of knee	3	3.0	3.0
(15) Dilation and curettage, cystocele and rectocele repair	6	2.5	2.5

* Orally, 1400 mg./dose.

TABLE 2

CLINICAL EVALUATION OF PAIN RELIEF RESULTING FROM THE ADMINISTRATION OF PLACEBO* IN POSTOPERATIVE SURGERY

Surgical procedure	Number of doses	Average of surgeon's impressions of relief of pain	Average of patient's impressions of relief of pain
(1) Cholecystectomy	3	1.7	1.3
(2) Wertheim hysterectomy and oophorectomy	1	1.0	1.0
(3) Bilateral lumbar sympathectomy and toe amputation	7	2.9	2.9
(4) Cholecystectomy and choledochostomy	2	0.0	0.0
(5) Hydrocele repair	3	1.0	0.3
(6) Inguinal hernia repair	1	3.0	3.0
(7) Cystoscopy, biopsy, and fulguration of bladder	2	0.0	0.0
(8) Appendectomy	5	2.2	2.2
(9) Dilation and curettage, pelvic repair, excision of thyroid adenoma	3	2.7	2.7
(10) Excision of ganglion of wrist	2	0.0	0.0
(11) Bilateral saphenous vein ligation and stripping	4	0.0	0.0
(12) Removal of toenail of big toe	1	3.0	3.0
(13) Ureterolithotomy	3	0.7	0.7
(14) Fulguration and excision of pilonidal sinus.	1	3.0	3.0
(15) Pyelolithotomy, cholecystectomy, and appendectomy	5	2.4	2.4

* Orally, 4 capsules.

for patients receiving carisoprodol was 1.7, based on the surgeon's impression, and 1.60, based on the patient's impression. The average relief score for placebo was 1.56, based on the surgeon's impression, and 1.50, based on the patient's impression. The average relief score for patients on meperidine was 2.34, based on the surgeon's impression and 2.34, based on the patient's impression. These scores are shown graphically in FIGURES 1 and 2.

TABLE 3

CLINICAL EVALUATION OF PAIN RELIEF RESULTING FROM THE ADMINISTRATION OF MEPERIDINE* IN POSTOPERATIVE SURGERY

Surgical procedure	Number of doses	Average of surgeon's impressions of relief of pain	Average of patient's impressions of relief of pain
(1) Revision of traumatic amputation of left arm	4	0.5	0.5
(2) Lumbar dorsal splanchniectomy and kidney biopsy	13	3.0	3.0
(3) Orchidectomy	1	3.0	3.0
(4) Urethrolithotomy	6	2.5	2.5
(5) Transurethral resection of prostate	11	3.0	3.0
(6) Pectenotomy, sigmoidoscopy, anal dilatation, excision of anal fissure	3	2.0	2.0
(7) Inguinal hernia repair and full-thickness graft to finger	4	1.3	1.3
(8) Cholecystectomy	7	2.7	2.7
(9) Inguinal hernia repair	2	3.0	3.0
(10) Cholecystectomy and appendectomy	14	3.0	3.0
(11) Pelvic repair	9	1.1	1.0
(12) Cholecystectomy	5	2.2	2.2
(13) Thyroidectomy	3	3.0	3.0
(14) Cholecystectomy, cystocele and rectocele repair	25	2.8	2.8
(15) Excision and plastic closure of axilla	1	2.0	2.0

* Orally, 100 mg./dose.

TABLE 4

SUMMARY OF RELIEF AFFORDED BY THREE TYPES OF CAPSULES

Average relief score	Total number of patients in each group					
	Carisoprodol (1400 mg.)		Placebo		Meperidine (100 mg.)	
	Surgeon's impression	Patient's impression	Surgeon's impression	Patient's impression	Surgeon's impression	Patient's impression
0 to 0.9	5	5	5	6	1	1
1 to 1.9	1	2	3	2	2	2
2 to 2.9	6	6	4	4	6	6
3.0	3	2	3	3	6	6

Discussion. Our results show no significant effect of carisoprodol on postoperative pain. Statistical comparisons of the average relief scores were made, using the Student's t distribution, and the results are shown in TABLE 5. Under this type of analysis a probability of less than 0.05 is usually considered a significant difference of the means. Therefore, the average relief score from the administration of 100 mg. per dose of meperidine is significantly greater than that of both 1400 mg. per dose of carisoprodol and placebo. The average relief score of 1400 mg. per dose of carisoprodol under this test is not significantly different from that of placebo.

It is interesting that, during the double-blind study, only 4 patients requested pain medication with sufficient frequency to receive more than 10 doses, and that all 4 of these patients were on meperidine, a drug known to produce habituation. The only marked side effect in the 45 patients of the

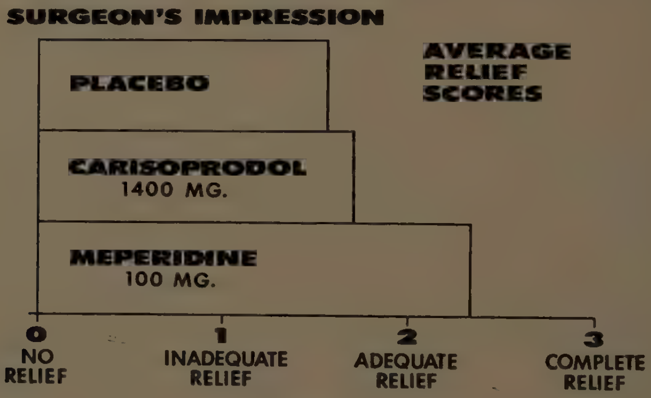

FIGURE 1.

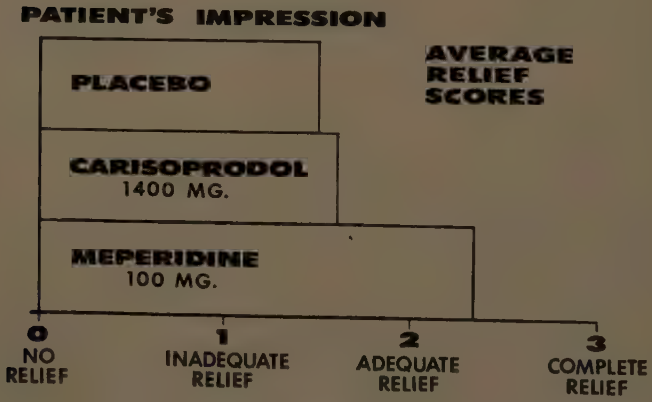

FIGURE 2.

TABLE 5

PROBABILITIES THAT TWO GIVEN MEDICATIONS HAVE THE SAME TRUE MEAN SCORE FOR THE RELIEF OF PAIN

	Meperidine (100 mg.) and placebo	Meperidine (100 mg.) and carisoprodol (1400 mg.)	Carisoprodol (1400 mg.) and placebo
Surgeon's impression	<0.025	<0.05	>0.35
Patient's impression	<0.025	<0.025	>0.40

double-blind study was severe drowsiness in one of the patients receiving carisoprodol.

Summary

In a double-blind evaluation of carisoprodol at a dose level of 1400 mg. in postoperative surgical patients, the compound did not exhibit a significantly greater analgesic effect than did the placebo, whereas meperidine at 100 mg. per dose exhibited a significantly greater analgesic effect than placebo.

In our experience carisoprodol at 1400 mg. per dose for short durations of therapy revealed no toxic effects, and the only side effect noted was severe drowsiness.

TABLE 6

TABULATION OF RESULTS OF FIRST DOSE ONLY AND TOTAL NUMBER OF PATIENTS IN EACH GROUP

Average relief score	Carisoprodol (1400 mg.)		Placebo		Meperidine (100 mg.)	
	Surgeon's impression	Patient's impression	Surgeon's impression	Patient's impression	Surgeon's impression	Patient's impression
0	6	6	5	5	1	1
1	1	1	2	2	4	4
2	4	4	1	1	3	3
3	4	4	7	7	8	8

APPENDIX

A comment by Louis Lasagna of Johns Hopkins University, Baltimore, Md., prompted a tabulation of the effect of only the first dose of medication given to each of the 45 patients in this study. The results are shown in TABLE 6, and one may see that, with minor variations, the same trend is apparent here as in TABLE 4. It is interesting to note that, on the basis of the first dose, 53 per cent of the patients receiving placebo and 53 per cent of the patients receiving carisoprodol obtained either adequate or complete relief from pain, while 73 per cent of those receiving meperidine received either adequate or complete relief.

THE RATIONALE OF TREATMENT OF MOTOR DISORDERS WITH MUSCLE RELAXANTS

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As one long experienced in assessing so-called muscle relaxants, I take the privilege of discussing several cogent issues in addition to offering an analysis of my results in the clinical evaluation of carisoprodol. For years I have been pleading for the use of a common terminology in the field, based on neurophysiology, so that we can compare the same things in our studies of patients. We are dealing with extremely complex and strikingly different physiological and biochemical entities not only when we contrast rigidity, spasticity, and athetosis, but even when we compare the same phenomena due to lesions at different levels. For example, spasticity due to complete section of the spinal cord at the level of the lumbar enlargement is a totally different pharmacological, electrophysiological, and biochemical entity from spasticity due to a lesion in a supraspinal segment. I labor this concept because I believe it is critically important. For example, we all accept tubocurarine as a specific and predictable muscle relaxant. Invariably, we observed that cases showing any suprasegmental control, no matter how little, could be made under some circumstance to show a reduction in spasticity when given curare in various long-acting suspensions. However, where a complete cord transection existed, a similar result could not be obtained until clinically impractical paralyzing doses were reached. The same observations held true for mephenesin, which we all accept as a potent muscle relaxant when used intravenously. The earliest paper published on this continent relating to the drug, by Stephen and Chandy (1947) submitted that mephenesin by vein did not affect spasticity in cord-transected cases. We were able to demonstrate to these investigators that in patients meeting their criteria excellent relaxation could be obtained, but at doses far higher than would have been efficient were there residual voluntary control. One can speculate at great length on the significance of these findings. I do not intend to indulge in such speculations. My point is merely to emphasize the importance of proper labeling and sorting so that rational comparisons may be made. A single mechanism cannot be isolated from a potpourri of mixed entities and used in comparison with the responses of other cases. The spasticity of an ataxic multiple sclerosis patient and the spasticity of an isolated-cord paraplegic patient may show totally different basic sensitivities to drugs. The exact site of pathology, its extent, and the nature of the remaining extrinsic influences determine the biokinetics of the neuronal pool and, finally, its abnormal manifestations and accessibility to drugs. Therefore, to assume that all cases are comparable because they share similar abnormal mechanisms and that they can be used as a group in analyzing drug effects is fallacious. It would be as illogical to try to deduce the hematopoietic effect of a compound after tabulating its performance in the anemia of blood loss, aplastic leukemia, neoplasia, and metabolic defect. Parenthetically, may I point out also that it will be necessary to ally the biochemical dimension of the problem more closely to the pharmacological and electrophysiological than in the past. So much has been learned about neuromuscular transmission in the last ten years, chiefly in the biochemical realm, that it is difficult to recollect that not many years ago the best we could say about the curare effect was that it created a sort of "Widensky inhibition."

My second point concerns methods of assessment of these compounds. These can be divided roughly into physiological methods, clinical methods, and the application of various statistical procedures to clinical methods. We have no quarrel with physiological studies in the laboratory. They are absolutely necessary and meaningful in terms of the preparations upon which they are carried out, and they form a basis for further clinical studies. One must remember, however, that many compounds with a good laboratory outlook show a remarkably poor level of clinical efficiency for many obvious reasons.

I am most concerned about the second and third approaches. We all have tried to arrive at a method of satisfactory objective appraisal of drug effects on motor disorders. First we go through the stage of electromyography and other laboratory methods of testing stretch response. Then, because of dissatisfaction with the results of our attempts to predict the integrated whole from the simple part, we go on to the cinematographic stage at which we carefully make seemingly comparable records of the patient before, during, and after the use of drugs. In the third stage, we reach the sophistication of the double-blind method which is more often, unfortunately, the blind leading the blind. Having been through all these stages, and having had the unusual opportunity of working in a well-endowed institution over a long period of years with the best of assistance and no pressures of any kind to weight the results, I can come to only one conclusion: that no clinical method seems nearly as valid as one involving measurements of functional efficiency. These measurements entail the use of a patient population with clear-cut diagnoses whose vicissitudes and divagations are well known so that they will not unduly influence the results. Such a stable of patients, along with sophisticated observers who handle the patients regularly without knowledge of their medication, affords an excellent compromise with all the dangers of clinical appraisal. In addition, it seems to me that the constant refining of testing techniques must attest, at least in part, to the subtlety of drug effect: no really potent compound would be so difficult to assess.

As to our clinical appraisal of carisoprodol: our group of twenty-eight patients included adults and children, all of whom had been known to us for as long as twelve years and were literally veterans in terms of drugs they had tried. Many of them had run the gamut from rum (which was the pharmacological choice of one of our research fellows) to such compounds as various barbiturates, hydantoins, erythroidines, and curares to drugs of the last decade whose names can best be epitomized as hopeful, shocking, tantalizing, or inscrutable. The neurological entities included athetosis, dystonia, spasticity of both cord and supratentorial origin, and painful muscle spasm. The compound carisoprodol, on initial screening, seemed to have pharmacological effects when taken by the oral route that made it worthy of further study. Our second observation was that at normal dosage levels it produced less drowsiness than meprobamate, and patients tended to become less drowsy after they had been on the drug for a short time. Surprisingly, no toxicities were revealed by careful blood and urine studies over periods of several months. The patients seemed considerably easier to evaluate than during comparable studies with meprobamate where the tranquilizer effect was so apparent that one could never be sure of the exact nature of the patient's improved performance. The patients themselves noted far less tranquilizer effect. Nevertheless, light headaches and grogginess were outstanding side effects at effective dosage levels. In the group of patients with athetoid dyskinesia there seemed to be no improvement over the results with meprobamate, where the tranquilizer effect of the latter seemed to be the basic reason for the improved performance. Puzzlingly enough, however, some of the patients on carisoprodol showed a most gratifying response to what we call the startle test for the response to sudden disturbing external stimuli—the buffering against external stimuli was not markedly tranquilizing. Performance tests included all of the well-known methods used in physical therapy for measuring abnormal stretch response. Strength, gait patterns, speed of performance, speech, and fatigability were all laboriously recorded. The patient's vocational achievement and efficiency throughout the various departments of the institution were charted. There seemed no question after compilation of the total data that carisoprodol showed a variably useful effect in the abatement of spasticity. This is not to say that there was any uniform response that could be predicted generally or even that the response would be obvious to an earnest but unsophisticated observer. Our physical therapists felt that patient performance in about one half the group with true spasticity was enhanced to a clinically perceptible point in terms of hand dexterity and gait activity and translated into the over-all efficiency of demands of daily living and vocation. Occasionally, performance speed attested to the accuracy of these clinical observations. In such cases performance could be brought to higher plateaus by habit training which, of course, is a goal of physical therapy. Brace work was easier and the minutiae of such studies as brace wear and tear, shoe wear and tear, and gait noise all seemed to corroborate the over-all clinical observations.

Summary

Although carisoprodol seems definitely to enhance potential opportunities for physical re-education and responses in some patients with spasticity, its effects are marginal and of an order apparent only to a trained observer. Nevertheless, in view of its lack of toxicity and relative usefulness compared to available alternatives, it seems to have a place in the rehabilitation program.

Its action in the amelioration of abnormal neuromuscular mechanisms cannot be ascribed solely to anxiety buffering, as seems to be the case with meprobamate.

Laboratory methods of testing for spasticity are almost surely doomed to failure as assays of clinical effects of muscle relaxants. Analysis of the effect of a compound on any single part of an organism does not necessarily reflect its action on the integrated whole. In the final analysis the brutal fact is that, of a superabundance of data and procedures, only time and large-volume clinical appraisal offer a final answer to usefulness and toxicity. A continuing attempt must be made to clarify the basic neurological entities described in

experimental and clinical studies, since only by this method will adequate comparative studies be valid and real insights obtained.

Since biochemical phenomena seem more likely eventually to clarify the nature of monitoring of motor function than conventional pharmacology or electrophysiology, it would be wise to incorporate the physicochemical dimension more closely into our thinking about the site of drug effects and the nature of mechanisms involved. In planning our clinical experiments we cannot necessarily extrapolate findings from electrophysiological techniques applied to accessible parts. For example, the response of muscle to electric stimulation does not necessarily reflect the total potentialities of the complex physicochemical pool at the site of pathology in the central nervous system, even though they are both bathed in varying concentrations of test drugs.

Reference

Stephen, C. R. & J. Chandy. 1947. Can. Med. Assoc. J. **57:** 463–468.

CLINICAL EVALUATION OF CARISOPRODOL IN HANDICAPPED CHILDREN

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The 83 handicapped children evaluated in this study consisted of 80 cerebral palsied children, 2 children with an unknown degenerating disease of the nervous system, and 1 child suffering from a tremor. In the cerebral palsied group there were 31 spastics, 13 rigidities, 34 athetoids, and 2 ataxics. All degrees of disability were represented. Most of the patients, however, were severe cases whose slow or negligible progress had caused them and their parents discouragement.

The etiology included midline developmental defects resulting in cerebral palsy, prematurity, Rh incompatibility, and difficulties at birth, including anoxia or hypoxia.

A rather large proportion of athetoids was purposely included in the group because the problem of care of such patients in the home is very great due to their constant motions.

In the original study, made in collaboration with Winthrop Phelps,* we found that in the 2 ataxic patients carisoprodol appeared to have too relaxing an effect and acted to make them extremely sleepy and flaccid. The drug was discontinued after about 3 weeks, and it was not tried with other ataxic patients. In no case was it reported that the drug had any untoward effect. In only 2 cases where an adequate regimen was administered was the medication reported to have no effect.

Dosage of carisoprodol was manipulated according to the effect on the child. Children under 5 years were started on one 250-mg. capsule daily; the dose was increased as tolerated. Patients over 5 and under 10 years of age were started on one 250-mg. capsule twice daily, and those over 10 years of age were started on one 250-mg. capsule 3 times a day. It was found that the children under 5 years needed one 3 times a day, and a few of the older children needed 250 mg. 4 times a day.

The only difficulty encountered in giving the 250-mg. capsule was caused by its size. First, the capsule was too large; and second, when the compound was removed from the capsule it proved to be very bitter. Masking the taste in syrups and juices was tried; finally, a multiple-vitamin syrup was used and found to be a good vehicle for administering the compound. In older children coating the capsule with butter made swallowing easier. Later, we changed to a 400-mg. tablet and, finally, to a 350-mg. sugar-coated tablet. The latter proved easiest to administer.

I made regular monthly examinations of the children. Blood counts and urinalyses were done and showed no change. Physical therapists and others treating the patients reported their observations. The parents of the patients and some of the patients themselves reported their findings.

All of the various data were compiled on each patient, and all except the ataxics experienced increased muscle relaxation and an improved psychological state far exceeding that previously obtained with such drugs as chlorpromazine, diphenylhydantoin, trihexyphenidyl, phenobarbital, and meprobamate. The children were happier, friendlier, and more willing to have their muscles stretched and limbs manipulated.

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Physical therapy made marked gains. Greater ease was noted in locking the braces, which could also be kept on for much longer periods. The children's muscles were more relaxed and easier to brace, and the children were happier and more willing to put up with the discomfort involved. The parents of these children were aided as well, because the children were easier to handle and care for in feeding, toileting, and dressing.

On re-examination of one patient I noted a decrease in deformities (probably the result of greater tolerance of corrective braces), a more rapid ability in attaining relaxation, and a greater length of time in maintaining it.

In the patients with rigidity carisoprodol improved sitting balance and disrupted the extensor thrust (a state of extreme muscle tension in which the head is thrown back, the back is arched, and sitting is impossible unless the patient is forced into flexion and thereby held in a sitting position). Many times it takes up to 2 years of various therapies to disrupt this extensor thrust. The reversed tongue movement that often accompanies cerebral palsy was lessened by carisoprodol, so that feeding became easier. The drooling that is characteristic of many patients with cerebral palsy was reduced markedly. Bowel and bladder control also improved.

Carisoprodol helped these patients, but the question arose: Could the drug be stopped and the gained muscle relaxation be maintained? Would the extensor thrust and tonic neck reflex return?

Wallace Laboratories, New Brunswick, N. J., produced placebos looking exactly like carisoprodol in 250-mg. capsule size to answer these questions. The parents and therapists were not informed of the change in medication. By the end of 2½ weeks the parents began complaining that the patients were awakening at night, crying with pain, and refusing to keep their braces on. The patients who had drooled excessively prior to using carisoprodol began to do so again. The children were irritable and fussed most of the day and night. The physical therapists reported that the drug was losing its effectiveness because the children seemed less relaxed and harder to work with in stretching their muscles. Some refused to stand in their standing tables, as they had previously done.

The placebos were continued for 4 to 6 weeks and then replaced by the new 400-mg. tablets of carisoprodol. After 1 week of the tablet therapy everyone who was working with and caring for these children had very good reports to give. The 400-mg. tablets were then replaced by 350-mg. sugar-coated tablets.

During the period of placebo therapy, physical examination showed the muscles to be more spastic than they were on carisoprodol therapy, but not as spastic as before the administration of the drug, so some gain had been made.

Two children who have an unknown degenerating disease of the nervous system and act like athetoids now have 90° of flexion in the ankles, whereas in the preliminary study they had obtained only 15° of flexion. Both of them are able to tolerate full control braces and are walking in parallel bars. Instead of seeming worse, they are better in that they are happier and most anxious to walk. Prior to the preliminary study they had regressed from independent walking to wheel chairs; now, after 22 months of carisoprodol, they never use wheel chairs.

Two of the cases of rigidity under 3 years of age, with marked extensor thrust and persistent tonic neck reflexes, lost their extensor thrusts after 3 to 6 months of carisoprodol therapy, and the tonic neck reflex disappeared at 6 months. These 2 children were not tried on placebos because their progress was so encouraging. Carisoprodol helped them to stay in flexion.

A 2-year-old child who had had a subdural hygroma removed 6 months prior to our study was placed on 250 mg. carisoprodol twice daily. This youngster had generalized flaccidity, but when she tried to walk she stiffened in all her extremities and seemed fearful. Carisoprodol was tried, and the patient became so listless that she did nothing but sit, so the drug was discontinued after 3 weeks. The patient never returned to her stiffening or fearfulness, but progressed to independent walking with the aid of braces and crutches. We do not know whether this can be attributed to coincidence or to carisoprodol.

All of these children were on wheat-germ oil, vitamin B_6 and a multiple-vitamin preparation, all of which were continued throughout all phases of the studies. Did this supplement the effectiveness of carisoprodol? Some clinicians have claimed that wheat germ and vitamin B_6 help the muscle tone.

In summarizing this study, I have found carisoprodol to be effective in the eight following ways: it (1) reduces the amount of drooling; (2) seems to relax the spastics so that corrective braces can be tolerated more readily and with lessened emotional strain; (3) appears to help the rigidities tolerate their corrective therapies; (4) disrupts extensor thrust and tonic neck reflex; (5) makes the children eager to try to ambulate; (6) helps correct the reversed tongue movement; (7) encourages better bladder and bowel control; and (8) makes activities of daily living more nearly normal.

CARISOPRODOL IN THE MANAGEMENT OF TEMPOROMANDIBULAR JOINT PAIN AND DYSFUNCTION: A PRELIMINARY INVESTIGATION

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In the medical and dental literature of the past twenty-five years many symptoms have been attributed to supposed malposition of the condylar head of the temporomandibular joint, particularly in the closed position. The symptoms described included loss of hearing, vertigo, and tinnitus, as well as pain in the temporomandibular joint. The usual explanation has been that, with missing posterior teeth, the condylar head of the temporomandibular joint causes pressure upward and backward upon various structures.

Anatomic and clinical investigations during the past 10 years, however, support neither this symptomatology nor the concept upon which it is based. The present widely held view is that temporomandibular joint pain and dysfunction constitute a symptom complex. Malocclusion, instead of being considered the prime or even the only etiological factor, is now more accurately considered as one of many contributing factors. Spasm of the masticatory muscles is felt to be at the root of the disorder. Hence, the symptom complex associated with the temporomandibular joint is similar to myofascial pain syndromes that affect other areas of the body.

The syndrome is most often found among women from 30 to 50 years of age. The most common complaint is that of a unilateral dull ache involving the face, temple, neck, and shoulder. Earache is a common complaint. In many cases clicking of the temporomandibular joint, its subluxation, or even actual dislocation, precede the actual limitation. When limitation is present, the mandible usually deviates toward the symptomatic side during the opening movement and sometimes also during protrusion. When dysfunction is present, the position of the jaw is sometimes so altered in its closed position as to cause a malocclusion of the teeth.

Symptomatology is usually noted: first, upon awakening, presumably because of tooth-clenching or -grinding while asleep; second, after rapid or continuous opening such as yawning or following a dental appointment; and third, subsequent to changes in proprioception accompanying any alteration of the occlusion of the teeth through dental treatment.

Upon clinical examination the most common findings are first, that mandibular movements are found to be limited and painful, and second, that masticatory muscles and temporomandibular joints are painful to palpation.

Radiographic examination of the temporomandibular joints usually discloses no alteration of their bony contours. There is a limited range of condylar movement in one or both joints.

In some cases spontaneous recovery occurs; in others, the symptoms continue for months and sometimes for years. A self-perpetuating pain-spasm cycle is believed to be operative. Emotional tension has been found to play a significant role.

Management

The six following methods of treatment are used generally: (1) use of local anesthetics in the form of the intramuscular injection of procaine or the spraying of ethyl chloride on the skin; (2) physical therapy, particularly the use of therapeutic exercises; (3) use of physical agents, such as the use of moist heat; (4) intra-articular injection of adrenal corticosteroids; (5) alteration of the occlusion of the teeth through dental treatment; and (6) use of drugs, especially muscle relaxants and analgesics.

A new drug, carisoprodol, has been described as having a specific effect on antigravity muscles, which suggests that it might be useful in treating the signs and symptoms of patients presenting with pain and/or dysfunction of the temporomandibular joint as mediated by spasm of the masticatory muscles. Carisoprodol appears to be about 8 times as potent as meprobamate or mephenesin in relaxing induced spasticity in animals, and it is described as effective in counteracting decerebrate rigidity that is not satisfactorily released by the older muscle relaxants. Carisoprodol has thus been recommended specifically for adult use in acute conditions of the musculoskeletal system characterized by pain, stiffness, and spasm.

TABLE 1

TREATMENT OF 10 PATIENTS WITH TEMPOROMANDIBULAR JOINT PAIN AND DYSFUNCTION WITH STRETCHING EXERCISES AND CARISOPRODOL*

Total number patients	Number of patients improved	Average increase mandibular opening	Number of patients with side effects
10	7	12 mm.	1

* Administered (1400 mg. daily) in divided dosage (Q6h) for 7 days.

Studies with Carisoprodol

Introductory clinical impressions. Carisoprodol (350 mg.) was prescribed 4 times daily for a period of 1 week to a group of 10 patients (seen in the private practice of one of us—L.S.) presenting with the temporomandibular joint syndrome described above. Three men and 7 women with an average age of 39 years for the males and 43 years for the females were studied (TABLE 1). The average duration of the symptoms was 9 months. The drug was prescribed after the diagnostic findings had been presented to the patient and after stretching exercises had been demonstrated and prescribed for home use. No local anesthetic procedures were utilized, although this therapeutic regimen with exercise is usually followed routinely whenever pain is present.

Seven patients reported improvement under this regimen. A clinical impression of objective improvement was also entertained following re-examination of these patients on the basis of an increased range of mandibular opening and a lessening of pain with mandibular movements and upon palpation of the temporomandibular joints and the masticatory muscles. Only one patient reported a side effect; she claimed that the pills "made her cranky."

A Controlled Study

Encouraged by these preliminary findings, a double-blind controlled study was undertaken in the Temporomandibular Joint Clinic of the School of Dental and Oral Surgery of Columbia University, New York, N.Y.

Methods. Thirty-four patients, 4 male and 30 female, with an average age of 34 years for the men and 41 years for the women, were studied (TABLE 2). All patients presented 1 or more of the above-described signs and symptoms of temporomandibular joint dysfunction. The average duration of the disorder was 15 months.

Twenty-eight tablets, each containing 350 mg. carisoprodol (the active agent) or 28 placebo tablets, formulations that had been provided by the manufacturer under code, were placed in consecutively numbered envelopes and distributed to patients at random. The code was not known to those who examined and prescribed for the patients. One tablet (either carisoprodol or placebo) was prescribed 4 times daily for 1 week.

TABLE 2

TREATMENT OF 34 PATIENTS WITH SYMPTOMS OF TEMPOROMANDIBULAR JOINT PAIN AND DYSFUNCTION WITH CARISOPRODOL:* A DOUBLE-BLIND CONTROLLED STUDY

Prescription	Total number patients	Number of patients improved	Average increase mandibular opening	Number of patients with side effects
Drug	17	5	8 mm.	5
Placebo	17	5	10 mm.	4

* Administered (1400 mg. daily) in divided dosage (Q6h) for 7 days.

No discussion of the investigators' diagnosis or conclusions concerning the patients' complaints was permitted prior to experimental therapy. In addition, in order to remove another group of variables from consideration, no other reatment, such as the use of exercise or local anesthesia, was instituted.

One week later the patients were re-examined clinically by the dentist who ad performed the original examination. These findings were reviewed by a second and independent examination.

Results. Of the 17 patients who received carisoprodol, 5 reported improvement subjectively and 12 reported no change. Of the 17 who received the lacebo, 5 reported improvement and 12 reported no change.

Clinical examination based on objective signs (range of mandibular opening, ain associated with mandibular movements, and palpation of the temporomandibular joints and masticatory muscles) revealed the following: in the arisoprodol-treated group of 17 patients, there was a clinical impression of improvement in 5 patients and no change in 12. In the placebo-treated group, which also consisted of 17 patients, there was a clinical impression of improvement in 6 patients and no change in 11. The average increase in mandibular opening in the group receiving carisoprodol was 8 mm., as opposed to 10 mm. in the placebo-treated group.

Following tabulation it was noted that those patients who had shown subjective and/or clinical improvement in either group had a history of having been troubled by symptoms for a shorter period of time than had those who had shown no improvement. Thus, the average duration of existent symptomatology in the group showing improvement with carisoprodol was 11 months as opposed to 6 months in the placebo group. The average duration of symptomatology of patients showing no improvement with either carisoprodol or placebo was 21 months.

Side effects were reported by patients in both the carisoprodol and the placebo groups, including 5 patients of 17 who received carisoprodol and 4 of 17 in the placebo group. Of the side effects reported, none of which were of consequence, the one most often reported in the carisoprodol-treated group was a feeling of drowsiness.

Discussion

Our double-blind controlled study provided clinical impressions at decided variance with those obtained through the first uncontrolled clinical trial. It would appear from the controlled study that carisoprodol had little if any beneficial action in this syndrome, based on a comparison of its effects with those following the administration of placebos. However, the total number of patients investigated and the brief period of observation of these patients precludes definitive conclusions other than those of a preliminary nature.

There are, nevertheless, other factors to be considered. The 10 patients studied to obtain initial clinical impressions were treated in private practice, with these 4 results: (1) the examination was conducted under a favorable atmosphere; (2) the full attention of the doctor was devoted to each patient without interruption; (3) the diagnostic impression that the symptoms were due not to organic disease but to muscle spasm was conveyed to the patient; and (4) the patient thus received both optimum attention and reassurance. Such latter measures, as Modell[1] points out, are of therapeutic value in the relief of skeletal muscle spasm not due to organic disease. All of these favorable circumstances may well be important in the management of the temporomandibular joint syndrome.

Contrariwise, the 34 patients included in the double-blind controlled study did not receive such attention; a common treatment room was utilized, the patients being examined simultaneously (and with interruptions) by different staff members, thus depriving the patients of exclusive attention; the diagnostic impression with reassurance was not provided the patient until he returned 1 week later, which was after the course of therapy.

In addition to the psychological influences resulting from the different conditions of the examination, physiological differences between the two studies had been introduced as well. In the initial study stretching exercises were demonstrated and prescribed for home use, whereas in the controlled study such exercises were not prescribed. This factor alone appears to be significant, perhaps because our clinical experiences point to the fact that exercise is a basic form of therapy for spasm of the jaw muscles. Anesthetics, physical agents, and drugs are also used, but these medications are looked upon as adjuncts that facilitate the return of the muscle fiber to normal length by relieving the pain, which has been aggravated by function.

The length of the duration of the symptoms may also be important since, usually, the shorter the duration of symptomatology the more easily reversible is the jaw-muscle spasm. For example, in the double-blind controlled study, as noted above, the average duration of symptoms of the patients who showed improvement was 11 months for the carisoprodol-treated group and 6 months for the placebo-treated group, as opposed to 21 months for the patients who showed no improvement.

Two further possibilities also must be considered: namely, that the drug may be active but (1) muscle spasm may not be the sole or major cause of this syndrome or (2) the over-all effectiveness or useful activity of carisoprodol in 1 or more of the cases may have been masked in a "statistical" sense by a large number of placebo reactors in this probably "unusually susceptible" group.

A more extensive study concerned with the use of carisoprodol with a larger group of patients under optimum conditions of care and reassurance but with a double-blind controlled technique might nevertheless prove of value, particularly if efforts were made to quantitate further the results by measuring the range of opening movement of the jaws more precisely and quantitating any improvement in the range of movement by temporomandibular joint roentgenograms.

Summary

Although an uncontrolled pilot study concerned with the use of carisoprodol in the treatment of the so-called temporomandibular joint syndrome appeared to be encouraging, a controlled double-blind study of 34 patients failed to corroborate such a favorable clinical impression.

A number of factors (other than the experimental technique) that may have caused the findings of the preliminary study of patients in private practice to have been at variance with those derived from the controlled study undertaken in a dental school clinic are considered.

Acknowledgment

The carisoprodol (Soma) tablets and placebo tablets utilized in this study were supplied in generous quantities by Wallace Laboratories, New Brunswick, N. J., through the courtesy of John Mote.

Reference

1. MODELL, W. 1955. Relief of Symptoms. Saunders. Philadelphia, Pa.

PHENYRAMIDOL IN OBSTETRICS AND GYNECOLOGY: A STUDY OF 200 CASES

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Dysmenorrhea, or painful menstruation, is the prime complaint of approximately 5 per cent of our patients. The symptoms range from mild to severe cramps. Frequently the severe cramps cause incapacitation to the extent that bed rest becomes necessary, creating a problem for housewives as well as for employed patients.

The proper treatment of dysmenorrhea always requires a complete physical examination (including pelvic examination), proper laboratory studies, and a careful consideration of the patient's psyche. My associates and I have prescribed the entire gamut of the pharmacopoeia—vitamin compounds, antispasmodics, uterine relaxants, and narcotics—with only average results.

I present here a study of 50 cases of severe dysmenorrhea for which phenyramidol* was prescribed. No controls were employed. All cases were observed carefully for at least 2 years, and some for as long as 7 years. Ages ranged from 16 to 34 years. Patients were instructed to take 200 to 400 mg. of phenyramidol as soon as menstrual cramps started, and to repeat the dose every hour as needed, taking no more than 3200 mg. in 24 hours. TABLE 1 shows results obtained in these 50 cases.

I cite one case from 45 in which good or excellent results were obtained: K.P., a 23-year-old white female student nurse, later a nurse, whom we observed for 3 years, had severe, incapacitating dysmenorrhea. For two years every specific medicine for the ailment had been prescribed with no success. She lost 1½ to 2 days valuable working time each period. She was placed on phenyramidol with immediate, excellent results. She proclaimed phenyramidol the best, and really the only, relief she had ever known, and said she suffered none of the attendant side effects of many of the previous medicines she had taken, especially the narcotics. She was pleased not to have to lose any more important working time. During a subsequent appendectomy, she was examined while anesthetized and, again, the absence of pelvic pathology was confirmed.

Many similar cases could be quoted. In two cases, however, the use of phenyramidol for relief of dysmenorrhea produced poor results. A.McC. was a 16-year-old white student nurse when first seen. Her suffering from dysmenorrhea had been so intense that morphine had been prescribed with fair results. During the 3-year nurses' training course she lost 30 days of duty, which of course had to be made up before she was issued her diploma. Phenyramidol was prescribed for her with no success. It was not possible to make pelvic examinations, but regular rectal examinations were made. No abnormality was discovered until 3 months before her graduation when, during an examination, a mass was palpated in the left ovarian area. Surgery revealed a dermoid cyst of the left ovary. Since surgery 1 year ago, she has been completely free of dysmenorrhea.

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* Furnished as IN511 by Irwin, Neisler & Co., Decatur, Ill.

The other case, M.M., was 31 years old, gravida III, para II, aborta I. This white female was first seen 7 years ago. Her history included an appendectomy and right ovarian cystectomy for dermoid cyst at 17 years. Since marriage at 25 years, she has had 3 pregnancies. One was a miscarriage and the other 2 produced full-term, living children. Four months after the last delivery she developed severe dysmenorrhea that could not be controlled by phenyramidol. Pelvic examination for 6 months revealed no abnormality, but subsequently her left ovary became enlarged and, still later, dysmenorrhea increased. Surgery revealed a hemorrhagic follicular cyst of the left ovary. This was enucleated, but ovarian function was conserved. Following operation, dysmenorrhea disappeared. She has been followed postoperatively for 1 year and has been found to be free of symptoms.

TABLE 1
PHENYRAMIDOL IN DYSMENORRHEA

Patients		Results		
		Excellent	Good	Poor
Number	50	40	5	5
Percentage	100	80	10	10

TABLE 2
PHENYRAMIDOL IN PREMENSTRUAL TENSION HEADACHES

Patients		Results		
		Excellent	Good	Poor
Number	50	35	5	10
Percentage	100	70	10	20

TABLE 3
CLINICAL COMPARISON OF PHENYRAMIDOL PLUS ASPIRIN WITH CODEINE AND ASPIRIN IN POSTPARTUM PATIENTS

	Phenyramidol with aspirin	Codeine with aspirin
Total patients	100	100
Side effects	1*	2†
Pain relief		
Excellent	80	79
Good	20	19
Poor	0	2†

* Due to patient's allergic reaction to aspirin; however, a good effect was obtained when phenyramidol alone was substituted.

† Due to patients' allergic reactions to codeine.

These 2 cases demonstrate actual pathology as the cause of dysmenorrhea. In 4 of the 5 failures of phenyramidol in the treatment of dysmenorrhea, 4 were failures because of pathology, and only 1 case failed to respond to the drug, for no apparent reason.

Phenyramidol was used in 50 cases of premenstrual tension headaches in women from 16 to 42 years of age. They were instructed to take 200 to 400 mg. of phenyramidol at the first symptom and to repeat in 1 hour as necessary. TABLE 2 illustrates the results.

One hundred consecutive postpartum patients were given a combination, in tablet form, of 200 mg. phenyramidol and 325 mg. aspirin as a substitute for 32.5 mg. codeine sulfate and 650 mg. aspirin, to determine whether the non-narcotic phenyramidol plus aspirin could be a satisfactory substitute for codeine and aspirin. The patients were unaware that a study was in progress, but were told that the medicine was for postpartum pain. This 1-month study is compared in TABLE 3 with 100 similar cases maintained on routine codeine and aspirin during the following month.

These results indicate that phenyramidol and aspirin can be substituted, in postpartum analgesia, for codeine and aspirin. One advantage of this substitution is economic, in that federal regulations on the administration of narcotics, which entail an expensive hospital procedure, do not apply.

Summary

Phenyramidol has been used in 200 cases. For the treatment of dysmenorrhea, excellent and good results were achieved in 45 of 50 cases and poor results in 5 cases (4 of which were accounted for by pathology). Thus only 1 poor result was noted in 46 cases (2.17 per cent). The analgesic effect combined with the apparent antispasmodic effect of phenyramidol is potent in the management of dysmenorrhea. From the cases studied, it may be concluded that a failure in the treatment of dysmenorrhea with phenyramidol will indicate almost invariably the presence of some pathology.

Phenyramidol in the treatment of premenstrual tension headaches gave excellent results in 35 of 50 cases, good results in 5 cases, and poor results in 10 cases. Five of the poor results were later re-evaluated as migraine attacks in which there was a great psychic overlay. Good and excellent results were obtained in 40 of 45 cases (88.9 per cent) and failures in 5 cases (11.1 per cent).

Results with phenyramidol and aspirin in 100 postpartum cases prove that phenyramidol may be substituted in postpartum analgesia for codeine and aspirin as used today.

Phenyramidol may be dispensed as simply as aspirin or mineral oil. In view of the time consumed by hospital nursing personnel and pharmacy staffs in handling the formalities involved in dispensing narcotics, the ease of dispensing phenyramidol is a welcome change.

Thus phenyramidol is an analgesic drug that does not require narcotic prescriptions; excellent results, as detailed above, have been noted in the treatment of dysmenorrhea, premenstrual tension headaches, and postpartum analgesia.

BIOCHEMICAL PHARMACOLOGICAL CONSIDERATIONS OF PHENYLBUTAZONE AND ITS ANALOGUES

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Phenylbutazone (Butazolidin) has three principal activities in man: it is a potent antirheumatic agent, causes marked retention of sodium, and possesses mild uricosuric properties.[1,2] Studies have been carried out both with metabolites of phenylbutazone and with various analogues of the drug in an attempt to find drugs of the phenylbutazone type with more potent properties useful for the treatment of various arthritic diseases.

Metabolism of Phenylbutazone

Initial studies showed that phenylbutazone is convered in man to two metabolites[3] (FIGURE 1). One product is formed by the introduction of a phenolic group in the para position of a benzene ring (Metabolite I), the other by the introduction of an alcohol group in the butyl side chain (Metabolite II).* These compounds are of considerable interest in relation to the activities of the parent drug.[6] Metabolite I has the potent antirheumatic and sodium-retaining effects of phenylbutazone. On the other hand, Metabolite II possesses little sodium-retaining and antirheumatic properties, but is considerably more potent as a uricosuric agent. In addition, there are marked differences in the rate of metabolism and in the extent of oral absorption of these metabolites in man. Metabolite I, like phenylbutazone, is metabolized slowly with a half life of about 72 hours, whereas Metabolite II is metabolized rapidly with a half life of about 12 hours (FIGURE 2). Again, like phenylbutazone, Metabolite I is well absorbed when given orally, whereas Metabolite II is not absorbed when administered by this route. Phenylbutazone and its two metabolites are extensively bound to plasma proteins, which accounts for their marked localization in the plasma compartment.

Physiological Disposition of Phenylbutazone Analogues

These observations on the metabolites of phenylbutazone suggested that it would be possible to influence markedly the pharmacological effects and physiological disposition of the drug by substitutions either in the benzene rings or in the butyl side chain. With this in view various analogues of phenylbutazone were synthesized† and their physiological disposition and pharmacological activity evaluated in man.

Marked differences were observed in the biological half life of the various phenylbutazone analogues (TABLE 1), as determined by measuring the plasma

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* The chemical synthesis of the two metabolites has been described.[4,5]

† We are grateful to F. Häfliger and his associates of J. R. Geigy Ltd., Basel, Switzerland, for the various phenylbutazone analogues used in this study.

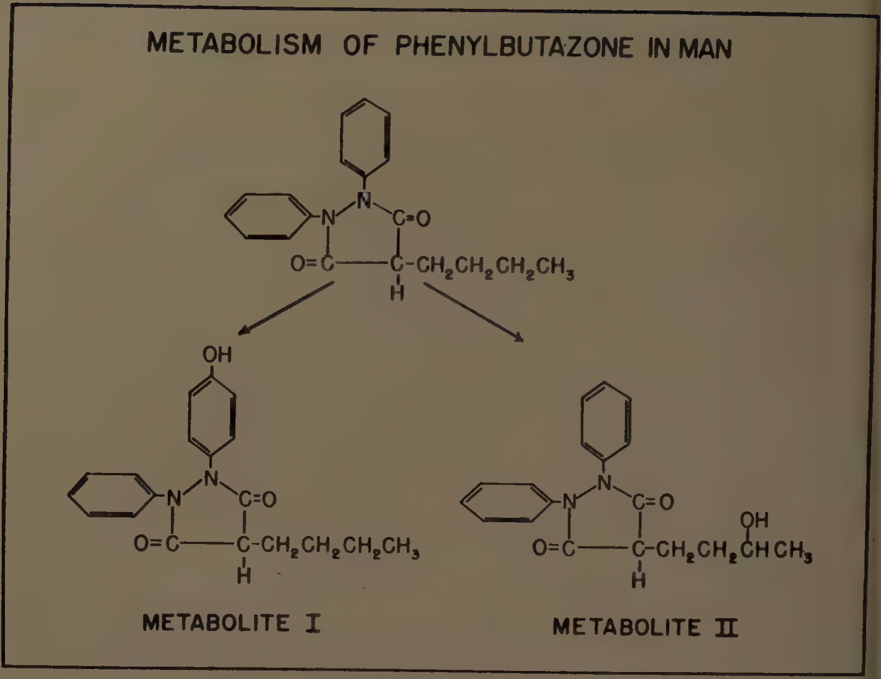


FIGURE 1. Metabolism of phenylbutazone in man.

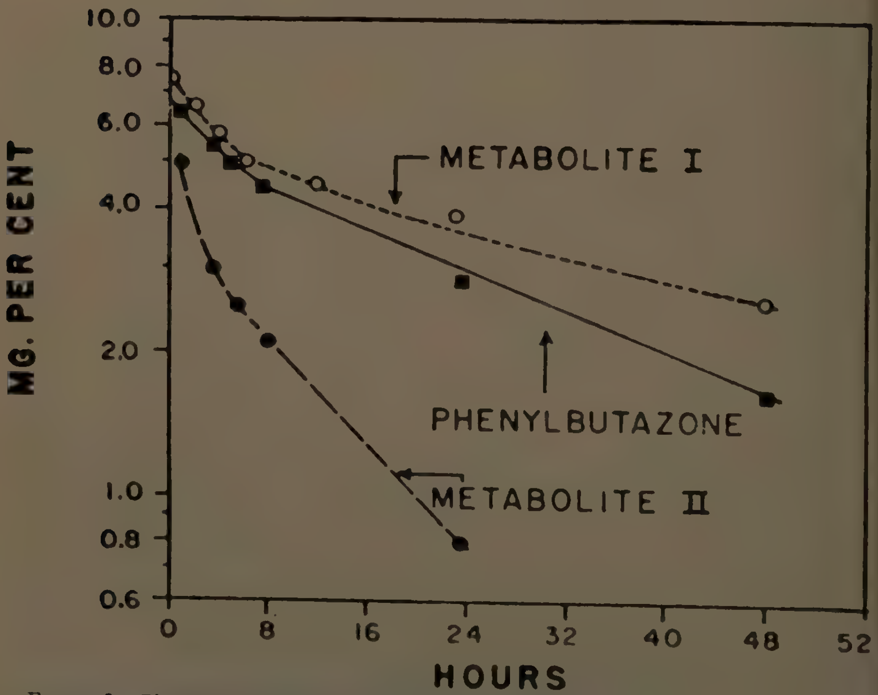


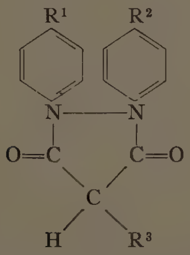
FIGURE 2. Plasma levels of Metabolite I, Metabolite II and phenylbutazone after a single 600-mg. intravenous dose of each compound to the same human subject.

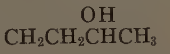
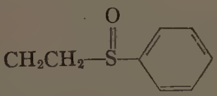
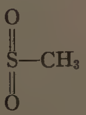
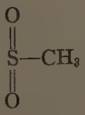
levels after intravenous administration of 600-mg. doses of the drugs to human subjects. It will be noted that the compounds disappear with a half life varying from 3 days for phenylbutazone to 1 hour for G-32567. The striking difference in the rate of disappearance of 2 phenylbutazone analogues that possess similar chemical structures is shown by the data in FIGURE 3.

The variations observed in the disappearance of phenylbutazone analogues in man are explained by differences in their rates of metabolism and excretion.[7] This is illustrated by the data given in FIGURE 4. Following the intravenous administration of phenylbutazone, plasma levels decline slowly (half life, 72 hours) and, essentially, none of the drug is excreted in urine. On the other hand, following the intravenous administration of a sulfoxide derivative of phenylbutazone (sulfinpyrazone), plasma levels decline rapidly (half life, 3 hours) and about 45 per cent of the drug is excreted in urine.

TABLE 1

RATE OF DISAPPEARANCE OF PHENYLBUTAZONE ANALOGUES IN MAN



Compound	R^1	R^2	R^3	Half life (hr.)
Phenylbutazone	H	H	$CH_2CH_2CH_2CH_3$	72
Metabolite I	OH	H	$CH_2CH_2CH_2CH_3$	72
G-15235	CH_3	CH_3	$CH_2CH_2CH_2CH_3$	24
G-28234	NO_2	H	$CH_2CH_2CH_2CH_3$	20
Metabolite II	H	H	 $CH_2CH_2\overset{OH}{CH}CH_3$	8
Sulfinpyrazone	H	H		2
G-32567	 $\overset{O}{\underset{O}{\overset{\|}{\underset{\|}{S}}}}-CH_3$	 $\overset{O}{\underset{O}{\overset{\|}{\underset{\|}{S}}}}-CH_3$	$CH_2CH_2CH_2CH_3$	1

About one third of the phenylbutazone analogues studied were either not absorbed when given by mouth or only incompletely so. This information, along with the data showing marked differences in the rate of metabolism and

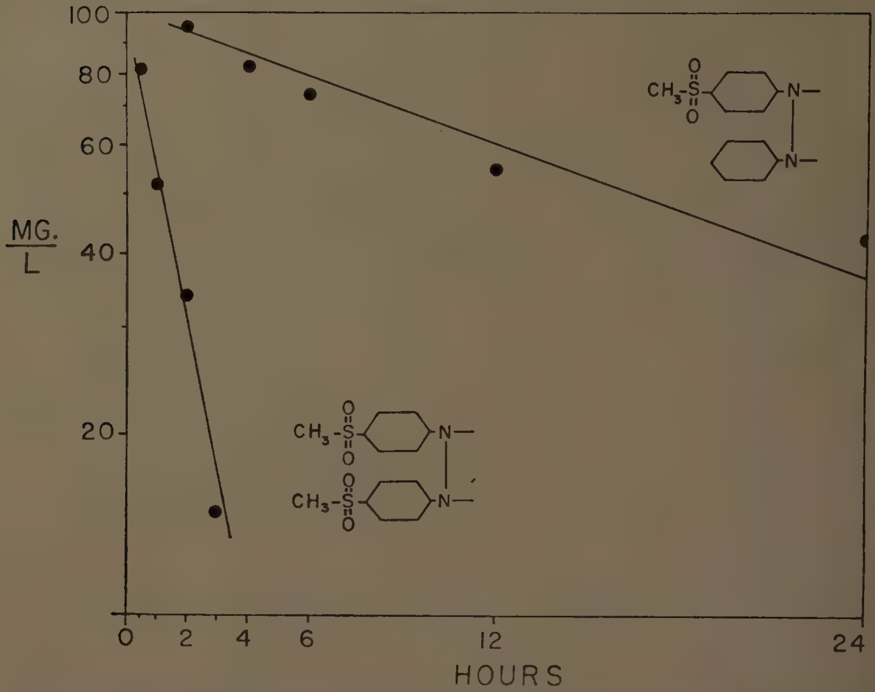


FIGURE 3. Plasma levels of a monomethyl sulfone derivative of phenylbutazone (G-34764) and a dimethyl sulfone derivative (G-32567) after a single 800-mg. intravenous dose of each compound to human subjects.

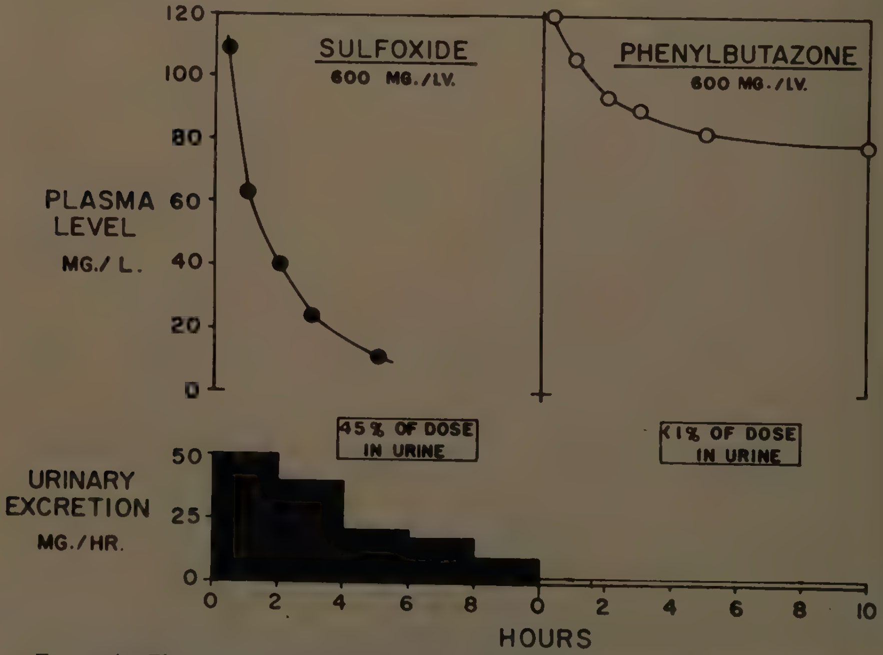
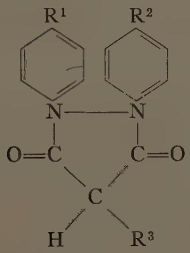


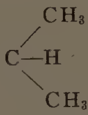
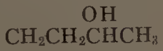
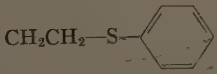
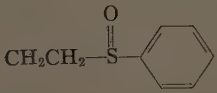
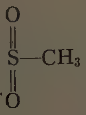
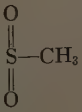
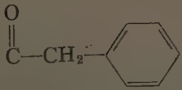
FIGURE 4. Plasma levels and urinary excretion of phenylbutazone and its sulfoxide derivative (sulfinpyrazone) following the intravenous administration of 600 mg. of each drug to the same human subject.

TABLE 2
SPECIES DIFFERENCES IN THE METABOLISM OF PHENYLBUTAZONE

Species	Biological half life
Man	72
Dog	6
Rabbit	3
Rat	6
Guinea pig	5
Horse	6

TABLE 3
ACIDITY AND URICOSURIC ACTIVITY OF PHENYLBUTAZONE ANALOGUES IN GOUTY SUBJECTS



Compound	R^1	R^2	R^3	Acidity (pK_a)	Dose of drug for uricosuric effect* (mg.)
G-13838	H	H		5.5	No effect with 1200
G-15235	CH_3	CH_3	$CH_2CH_2CH_2CH_3$	4.9	No effect with 1200
Metabolite I	OH	H	$CH_2CH_2CH_2CH_3$	4.7	800–1000
Phenylbutazone	H	H	$CH_2CH_2CH_2CH_3$	4.5	800–1000
Metabolite II	H	H	 $CH_2CH_2\overset{OH}{C}HCH_3$	4.0	150–300
G-25671	H	H		3.9	150–300
G-28234	NO_2	H	$CH_2CH_2CH_2CH_3$	3.2	30–100
Sulfinpyrazone	H	H		2.8	30–70
G-32567	 $\underset{O}{\overset{O}{S}}-CH_3$	 $\underset{O}{\overset{O}{S}}-CH_3$	$CH_2CH_2CH_2CH_3$	2.7	100–150
G-30249	OH	H		2.0	30–70

* The intravenous dose required to elicit a 100% increase in $C_{\text{uric acid}}/C_{\text{inulin}}$.

excretion of the various analogues, is of course essential in estimating the potential usefulness of the various drugs in patients.

Pronounced species differences were also observed in the rate of metabolism of phenylbutazone[8] (TABLE 2). This information is of importance for the interpretation of animal data. For instance, in order to achieve plasma levels of phenylbutazone in rats similar to those obtained in man, about fifteen times the dose of the drug on a per-kilogram basis must be administered. Species differences were also observed in the metabolism of the various phenylbutazone analogues.

Pharmacological Activities of Phenylbutazone Analogues

Considerable differences were observed in the pharmacological activities of phenylbutazone analogues in man. Substitutions of a chloro, methyl, or nitro group in the para position of the benzene ring result in compounds possessing potent antirheumatic and sodium-retaining activity. In contrast, substitutions of various groups in the meta position of the benzene ring or in the butyl side chain result in compounds that have little or no antirheumatic and sodium-retaining activity.

In general, it was found that modifications in phenylbutazone that increase the acidity of the molecule are associated with enhanced uricosuric activity, whereas changes that decrease the acidity of the drug are accompanied by loss of this activity.[9] In TABLE 3 are given the pK_a and relative uricosuric activity of a variety of analogues representing modifications either in the benzene rings or in the butyl side chain of phenylbutazone. It will be noted that the isopropyl analogue (G-13838) and the *p*-dimethyl analogue (G-15235), the weakest acids in the series, had no detectable uricosuric effect in the intravenous doses of 1200 mg. Phenylbutazone and Metabolite I required intravenous doses of 800 to 1000 mg. to elicit a 100 per cent increase in uric acid clearance, whereas Metabolite II and G-25671 produced this effect in doses ranging from 150 to 300 mg. Sulfinpyrazone and G-30249, two of the strongest acids, were active in doses as low as 30 mg. These results indicate that it is possible to predict uricosuric potency in the phenylbutazone series by a simple measurement of the acidity (pK_a) of the compound. The potent uricosuric activity of the highly acidic phenylbutazone analogues suggests that these drugs act in the ionic form to block reabsorption of uric acid by the renal tubule cells, thus furnishing a possible clue to the still obscure nature of the transport mechanisms involved.

The strongly acidic para-nitro analogue of phenylbutazone, G-28234 (FIGURE 5), possesses potent antirheumatic, sodium-retaining, and uricosuric properties.[10] This is, in fact, the first compound synthesized in this series to exhibit the three effects of phenylbutazone to a marked degree. These findings are in accord with the structural-activity relationships formulated in this series.

New Drugs for Arthritis and Gout

Several new drugs have been uncovered thus far in this program which may be of value in the treatment of various arthritic diseases (FIGURE 6). One such drug is the para-hydroxy metabolite of phenylbutazone (Metabolite I, oxyphenbutazone, G-27202) which is now undergoing clinical trials as an antirheumatic agent for the treatment of acute rheumatoid arthritis and acute gout.[6,11,12,13,14] Our own experience indicates that, in divided daily dosage of 800 mg., the drug is usually effective in terminating acute gouty attacks. Thus, of 145 attacks treated with oxyphenbutazone, complete remission within 24 to 48 hours was obtained in 79 per cent, complete remission within 1 week in an additional 12 per cent, a partial response in 5 per cent, and 4 per cent were refractory. These results do not differ significantly from those obtained with phenylbutazone or colchicine.

Another useful drug is a sulfoxide metabolite formed in man from a thioether derivative of phenylbutazone,[15] G-25671 (FIGURE 7). This sulfoxide metabolite (sulfinpyrazone), one of the most potent uricosuric drugs known, is now being used for the treatment of chronic tophaceous gout.[16-18] The uricosuric potency of the drug is indicated by comparison with other uricosuric agents in respect to the minimum dose required to elicit a significant increase in urate clearance.[19] This is of the order of 15 to 50 mg. for zoxazolamine; 35 to 50 mg. for sulfinpyrazone; 100 to 120 mg. for probenecid; 150 mg. for G-25671; 700 mg. for phenylbutazone, and 1000 mg. for salicylate. It should not be inferrred that these renal clearance data necessarily reflect the relative clinical efficacy of these drugs, which must be established by clinical trial. Our therapeutic results with sulfinpyrazone in gouty subjects (TABLE 4) support the clearance data in demonstrating its marked uricosuric potency. The side reactions thus far noted with sulfinpyrazone are similar in nature and incidence to those observed with probenecid (TABLE 5).

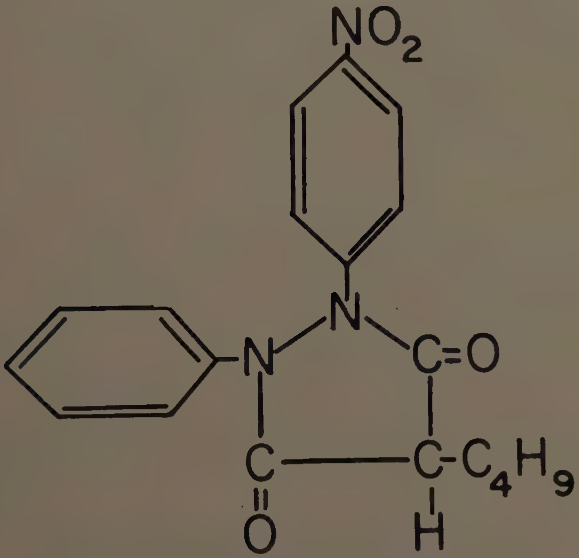
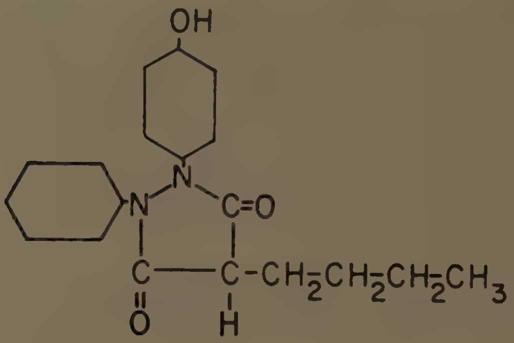


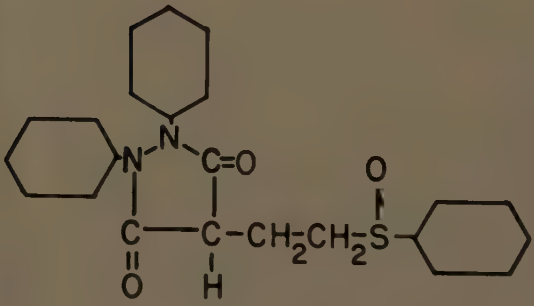
FIGURE 5. Para-nitro analogue of phenylbutazone.

Two other drugs have properties that suggest their potential use as potent



METABOLITE I (G-27202)

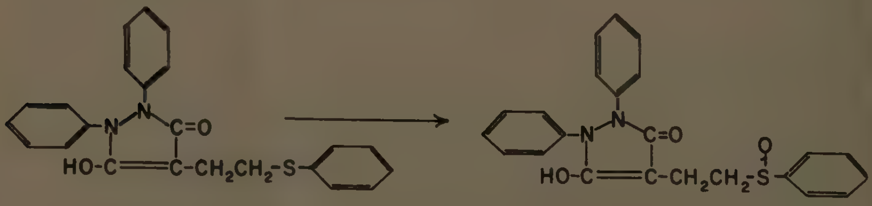
(OXYPHENBUTAZONE)



SULFOXIDE METABOLITE

(SULFINPYRAZONE)

FIGURE 6. Metabolism in man of a thio-ether derivative of phenylbutazone (G-25671) to a sulfoxide (sulfinpyrazone).



G-25671 (G-1)

SULFOXIDE METABOLITE (G-28)

FIGURE 7. New drugs in the phenylbutazone series.

uricosuric agents in the treatment of gout. One compound, a mono-methyl sulfone derivative of phenylbutazone (G-34764) is metabolized very slowly in man (FIGURE 3) and consequently exerts a prolonged uricosuric effect.[20] The other drug, an α-keto analogue of oxyphenbutazone (G-29701) also shows a persistent uricosuric effect.[21] Drugs that would exert prolonged uricosuric effect may be of considerable value in the treatment of gout, since their use would make unnecessary the frequent medication required in therapy with rapidly metabolizing drugs such as sulfinpyrazone and zoxazolamine.

TABLE 4

MOBILIZATION OF GOUTY TOPHI BY PROTRACTED USE OF SULFINPYRAZONE

Duration of therapy (years)	No. of cases	Reduction in size of tophi		
		No change	Slight or moderate	Marked or complete
0.5–1	18	12	4	2
1–2	6	2	1	3
2–3	10	0	3	7
Totals:	34	14	8	12

TABLE 5

SIDE REACTIONS TO SULFINPYRAZONE AND PROBENECID IN GOUTY SUBJECTS

	Sulfinpyrazone		Probenecid	
	No.	Per cent	No.	Per cent
Renal calculus or colic	7	10	15	8
Precipitation of acute attacks	5	7	16	9
Gastric distress	5	7	13	8
Skin rash	0	0	8	5

Summary

The results of this study show that it is now possible to relate changes in the antirheumatic, sodium-retaining, and uricosuric effects of phenylbutazone in man to certain changes in chemical structure of the drug. This information has been of aid in searching for new drugs in this series. So far, two new drugs have been subjected to intensive clinical study: Metabolite I (oxyphenbutazone), a potent antirheumatic agent in acute gout and rheumatoid arthritis, and a sulfoxide derivative (sulfinpyrazone), a potent uricosuric agent for the treatment of chronic tophaceous gout.

References

1. BRODIE, B. B., E. LOWMAN, J. J. BURNS, P. R. LEE, T. CHENKIN, A. GOLDMAN, M. WEINER & J. M. STEELE. 1954. Observations on the antirheumatic and physiologic effects of phenylbutazone (Butazolidin) and some comparisons with cortisone. Am. J. Med. **16:** 181.
2. YÜ, T. F., J. H. SIROTA & A. B. GUTMAN. 1953. Effect of phenylbutazone (3,5-dioxo-1,2-diphenyl-4-N-butylpyrazolidine) on renal clearance of urate and other discrete renal functions in gouty subjects. J. Clin. Invest. **32:** 1121.

3. Burns, J. J., R. K. Rose, S. Goodwin, J. Reichenthal, E. C. Horning & B. B. Brodie. 1955. The metabolic fate of phenylbutazone (Butazolidin) in man. J. Pharmacol. Exptl. Therap. **113:** 481.
4. Denss, R., F. Häfliger & S. Goodwin. 1957. Über Derivate des Phenylbutazons. II. Derivate mit einer Hydroxylgruppe in der 4-ständigen Seitenkette. Helv. Chim. Acta. **40:** 402.
5. Pfister, R. & F. Häfliger. 1957. Über Derivate des Phenylbutazons. I. In den Benzolkernen hydroxylierte Derivate. Helv. Chim. Acta. **40:** 395.
6. Yü, T. F., J. J. Burns, B. C., Paton, A. Gutman & B. B. Brodie. 1958. Phenylbutazone metabolites: antirheumatic, sodium-retaining and uricosuric effects in man. J. Pharmacol. Exptl. Therap. **123:** 63.
7. Dayton, P. G., L. Berger, T. F. Yü, L. E. Sicam, M. A. Landrau, A. B. Gutman & J. J. Burns. 1959. Relationship between pK_a and renal excretion of various phenylbutazone analogues. Federation Proc. **18:** 382.
8. Burns, J. J., R. K. Rose, T. Chenkin, A. Goldman, A. Schulert & B. B. Brodie. 1953. The physiological disposition of phenylbutazone (Butazolidin) in man and a method for its estimation in biological material. J. Pharmacol. Exptl. Therap. **109:** 346.
9. Burns, J. J., T. F. Yü, P. G. Dayton, L. Berger, A. B. Gutman & B. B. Brodie. 1958. Relationship between pK_a and uricosuric activity in phenylbutazone analogues. Nature. **182:** 1162.
10. Yü, T. F., J. J. Burns, P. G. Dayton, A. B. Gutman & B. B. Brodie. 1959. A p-nitro analogue of phenylbutazone possessing potent antirheumatic, sodium-retaining and uricosuric properties. J. Pharmacol. Exptl. Therap. **126:** 185.
11. Brodie, B. B., J. J. Burns, B. C. Paton, J. M. Steele, T. F. Yü & A. B. Gutman. 1956. Isolation, identification and physiological effects of phenylbutazone metabolites. Contemporary Rheumatol. **:** 600.
12. Hart, F. D. & D. Burnley. 1959. Phenylbutazone and its derivatives with special reference to G-27202. Brit. Med. J. **1:** 1087.
13. Vaughn, P. P., D. S. Howell & I. M. Kiem. 1959. The comparative effects of phenylbutazone and G-27202 (Metabolite I) in patients with rheumatoid arthritis: an assessment of methods for antirheumatic drug evaluation. Arthritis and Rheumatism. **2:** 212.
14. Cardoe, N. 1959. Controlled trial of G-27202 (p-hydroxy-phenylbutazone) in rheumatoid arthritis. Ann. Rheumatic Diseases. **18:** 244.
15. Burns, J. J., T. F. Yü, A. Ritterband, J. M. Perel, A. B. Gutman & B. B. Brodie. 1957. A potent new uricosuric agent, the sulfoxide metabolite of the phenylbutazone analogue, G-25671. J. Pharmacol. Exptl. Therap. **119:** 418.
16. Ogryzlo, M. A. & J. Harrison. 1957. Evaluation of uricosuric agents in chronic gout. Ann. Rheumatic Diseases. **16:** 425.
17. Kersley, G. D., E. R. Cook & D. C. J. Tovey. 1958. Value of uricosuric agents and in particular of G-28315 in gout. Ann. Rheumatic Diseases. **17:** 326.
18. Yü, T. F., J. J. Burns & A. B. Gutman. 1958. Results of a clinical trial of G-28315, a sulfoxide analog of phenylbutazone, as a uricosuric agent in gouty subjects. Arthritis and Rheumatism. **1:** 532.
19. Burns, J. J., T. F. Yü, L. Berger & A. B. Gutman. 1958. Zoxazolamine, physiological disposition, uricosuric properties. Am. J. Med. **25:** 401.
20. Yü, T. F., P. G. Dayton, A. B. Gutman & J. J. Burns. 1960. A methyl-sulfone derivative (G-34764) of phenylbutazone with prolonged uricosuric effect. Federation Proc. In press.
21. Seegmiller, J. E., P. G. Dayton & J. J. Burns. 1959. Physiological disposition and uricosuric effect of a keto analogue of oxyphenbutazone (G-29701). Abst. Meeting of the Am. Rheumatism Assoc. (December 11). Detroit, Mich.

THE PHARMACOLOGY OF PHENYLBUTAZONE ANALOGUES

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Chemical synthesis in the pyrazole series goes back as far as the description of antipyrine by Knorr in 1883.[30] The use of pyrazoles in medicine was confined for many decades chiefly to the compounds aminopyrine and antipyrine, the therapeutic effects of which were ascribed by Schottmüller[48,49] to the presence of analgesic, antipyretic, and antiseptic properties. Interest in the pyrazoles was rekindled as a result of the synthesis of the pyrazolidine derivative phenylbutazone by Stenzl *et al.*[53] and its introduction in therapy in 1948 by Wilhelmi and Domenjoz,[12-14,59,60,68,69] Pulver,[39] and Gsell and Müller.[25] The pharmacological investigation of phenylbutazone by Wilhelmi and Domenjoz[12-14,69] led to the realization that the therapeutic activity of the pyrazolidines in rheumatic diseases was based not on their analgesic and antipyretic properties, but on a specific anti-inflammatory effect. Our understanding of the mode of action of phenylbutazone has been advanced particularly by studies in the field of chemical pharmacology undertaken by Brodie and Burns[3-10] and by Pulver.[39-42] Phenylbutazone can be epitomized as a drug whose therapeutic effect is due less to its qualitative activity spectrum than to the special features of its biotransformation. The experience gained thus far with the pyrazolidine group constitutes impressive support for the view that, in the experimental evaluation of new drugs, the classic methods of pharmacology must be supplemented by an investigation of the quantitative, that is, the chemical conditions for their activity. The pharmacological actions of the pyrazoles can be demonstrated, in the main, only in the whole animal; the results obtained represent an integration of various factors: namely, activity, resorption, excretion, distribution, and breakdown, and do not permit any conclusion as to the mechanisms involved. This circumstance is of the utmost importance in developing new therapeutic agents, since inactivity, as adjudged on the basis of animal experiments, may be a result of metabolic peculiarities of the animal and thus, in principle, may be invalid for man. Indeed, the pharmacologist can attribute many of his disappointments to the differences in metabolism between man and the usual laboratory animals.

The chemical and pharmacological studies of Brodie and Burns and their colleagues on phenylbutazone and its derivatives may be summarized as follows:

(1) The discovery of the surprisingly slow rate of phenylbutazone's biotransformation in the human organism (corresponding to a half life of 72 hours), together with the demonstration of its binding to plasma proteins, have given an important insight into its conditions of action and have facilitated quantitative therapy.[3,5,6]

(2) Studies in the biotransformation of phenylbutazone and of the sulfur-containing analogue G 25671 have raised the question of whether metabolites must be regarded as actually responsible for the activity of the parent substances.[4,7-9]

(3) Studies made by these authors comparing pure metabolites with a series

of related compounds have provided the basis for the therapeutic utilization of oxyphenbutazone and have led to the discovery of the intense uricosuric activity of sulfinpyrazone.[9,10,73]

The present report deals with the pharmacology of oxyphenbutazone, of sulfinpyrazone, and of phenylbutazone. The Brodie group[7-9] has shown that phenylbutazone in the animal and human organism is broken down in two different ways, as shown in FIGURE 1: (a) hydroxylation of a benzene ring in the *para* position yielding metabolite I, oxyphenbutazone; (b) hydroxylation of the butyl side chain in the 3-position yielding metabolite II, G 28231.*

Of these two metabolites, oxyphenbutazone is the more important both quantitatively and, particularly, on account of its pharmacological properties. In spite of its phenolic structure, this compound is extraordinarily resistant to metabolic influences and has a biological half life in man of 2 days.[7]

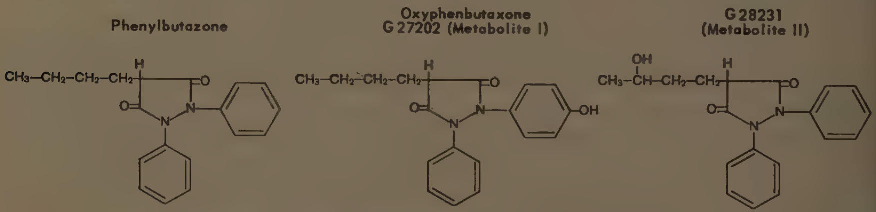

FIGURE 1. Phenylbutazone and metabolites I and II.

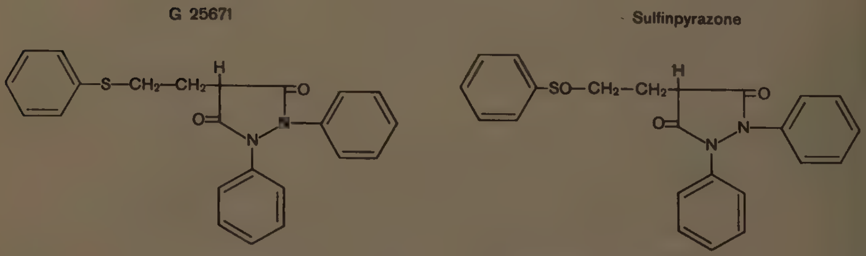

FIGURE 2. G 25671 and metabolite.

Under conditions of chronic administration, particular importance can be ascribed to this metabolite with respect to phenylbutazone activity. As Herrmann[27] has shown, the serum concentration of the metabolite after normal doses of phenylbutazone can attain therapeutically active levels. The pharmacological properties of oxyphenbutazone have been described by Burns *et al.*[7,8] and by Wilhelmi;[65] its clinical effects have been reported on by Connel and Rousselot,[11] Vaughan and Howell,[57,58] Mason and Cramer,[33] O'Reilly,[35] and others.

The sulfoxide sulfinpyrazone was identified as a metabolite of 4-(phenylthioethyl)-1,2-diphenyl-3,5-pyrazolidine-dione (G 25671) by Brodie *et al.*[4] (FIGURE 2). Experimental and clinical studies on G 25671 have been pub-

* The synthetic work concerning the metabolites mentioned, including the substance G 25671, was done by F. Häfliger and his collaborators of the Research Department of I. R. Geigy Ltd., Basel, Switzerland.[76-79]

lished by Burns *et al.*,[9] Wilhelmi and Currie,[67] Yü *et al.*,[74] Paton *et al.*,[36] and Kuipers and Tazelaar-Onderwater.[32] This substance, too, is a metabolite with interesting pharmacological properties. The rate of metabolic breakdown of the sulfoxide in man is the same as that of the parent compound and corresponds to a biological half life of 3 hours.[9]

Clinical studies on sulfinpyrazone, in particular as regards its therapeutic efficiency in gout, have been made by Gutman and Yü,[26] Kersley *et al.*,[29] and by Serre *et al.*[51]

EXPERIMENTAL

The most important therapeutic aspects of the pyrazoles and pyrazolidines involve their analgesic, antipyretic, and anti-inflammatory effects and their ability to enhance uric acid excretion. These different properties are found in differing degrees in many members of this group, but only in a few derivatives are any of them sufficiently marked and sufficiently selective to be therapeutically useful.

TABLE 1

MEDIAN LETHAL DOSES (MG./KG.)

	Mouse		Rat		Rabbit
	I.V.	Oral	I.V.	Oral	I.V.
Phenylbutazone	112	680	150	1280	146
Oxyphenbutazone	52	480	68	980	104
Metabolite II	623	>5000	—	—	—
G 25671	178	560	190	450	100
Sulfinpyrazone	240	298	154	375	195
Aminopyrine	205	748	140	1030	156

Toxicity

Median lethal doses. Acute toxicity has been measured in mice, rats, and rabbits for both intravenous and peroral administration. With mice and rats, groups of at least 10 animals (usually 20) per dose were used and, with rabbits, groups of 5 animals. The observation period was 8 days for intravenous administration, 14 days for the oral route. The median lethal dose, LD_{50}, was estimated graphically by use of the Gauss integral.

Comparison of the toxicity values for oxyphenbutazone and phenylbutazone reveals that no reduction of toxicity occurs as a result of this first step of biotransformation. In fact, the metabolite is markedly more toxic than the parent substance. This is especially apparent in the median lethal doses administered intravenously.

As the examples given in TABLE 1 show, the relation between the intravenous and oral LD_{50} is particularly interesting. For phenylbutazone and its metabolite, the ratio of oral to intravenous LD_{50} lies between 14.4 (oxyphenbutazone, rats) and 6.07 (phenylbutazone, mice). Quite a different result is shown by G 25671 and particularly by sulfinpyrazone. In the case of the sulfoxide, the I.V. LD_{50} is surprisingly close to the oral LD_{50}, the ratio being 1:2. This result indicates clearly that, after oral intake, sulfinpyrazone undergoes rapid and quantitative absorption, in contrast to the phenylpyrazone group. This result must be attributed to the solubility properties of the compounds concerned.

TABLE 2
SOLUBILITY* CONDITIONED BY *p*H

Solvent	*p*H	Phenylbutazone	Oxyphenbutazone	G 25671	Sulfinpyrazone
Phosphate buffer, 0.066 *M*	7.0 6.0	188 34.5	195 66	25 3.2	751 251
Acetoacetate buffer, 0.10 *M*	4.7 4.1 3.5	3.6 2.3 1.9	13.2 9.6 8.1	0.35 0.22 0.16	75.2 35.4 8.6
Distilled water		1.5	13.9	2.0	12.4

* In mg. per 100 ml. buffer solution.

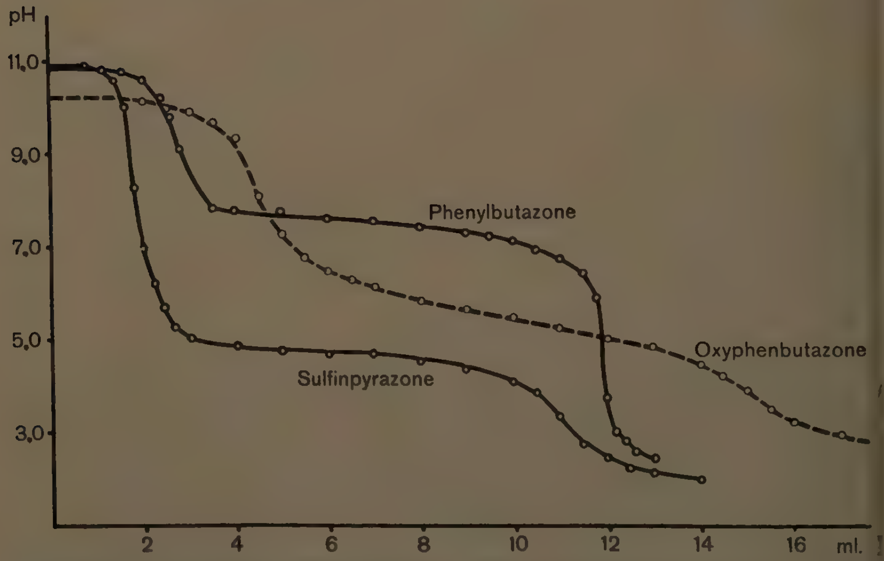

FIGURE 3. Electrometrical titration against *n*-HCl of phenylbutazone, oxyphenbutazone, and sulfinpyrazone.

The solubility of phenylbutazone and its analogues has been studied in detail by Pulver *et al.*[40,41] Using phosphate and acetoacetate buffers of various *p*H values, these authors prepared saturated solutions and determined the concentrations photometrically. The results are summarized in TABLE 2.

In a complementary study, Pulver *et al.*[40] performed electrometric titration of phenylbutazone, oxyphenbutazone, and sulfinpyrazone (FIGURE 3). In the case of phenylbutazone and sulfinpyrazone, 0.01 mole was mixed with 0.012 mole NaOH and titrated with *n*-HCl in a volume of 100 ml. water. In the case of oxyphenbutazone, the proportion was 0.001 mole to 0.0015 mole NaOH, and both titration with *n*-HCl and the establishment of a continuous titration curve were possible only with the addition of 35 per cent ethanol. With the compound G 25671 a continuous titration curve could not be recorded, even with 50 per cent ethanol.

The solubility of phenylbutazone and, particularly, its marked increase in this respect at *p*H 6.0 and above indicate, according to Pulver *et al.*,[41] that conversion to the salt-forming enol form occurs even in weakly acid and neutral solutions. Phenylbutazone probably circulates in blood in this hydrophilic form.

In the case of oxyphenbutazone, formation of the enol form occurs in a slightly more acid reaction. The sulfoxide behaves quite differently, in that the decisive change in solubility occurs between *p*H 3.5 and 4.0.

The properties revealed by these peculiarities are, of course, a result of the acidity of the molecules, as discussed by Burns *et al.*[10]

These authors showed that a distinct relationship exists between pK_a and uricosuric activity for a certain series of phenylbutazone analogues. In regard to the lethal doses for oral administration, the pK_a of the molecule also appears to be significant for solubility and, by this means, it also affects absorption of the compound from the gastrointestinal tract.

As regards toxicity symptoms, the studies revealed no difference between the different compounds, the visible effects being much the same in all cases. In the initial stage there were observed signs of central nervous stimulation such as rapid breathing, tremor, and convulsions with opisthotonus; later on, ataxia and stupor were recorded. The interpretation of the last-named symptoms would require investigation of the circulatory functions.

Subchronic Toxicity

Subchronic toxicity under conditions of daily administration was determined on groups of at least 10 rats (usually 20) per dose. The drugs were administered by stomach tube over a test period of 4 weeks. The daily doses were roughly 1/16, 1/8, 1/4, and 1/2 mg. of the acute oral lethal dose.

The results of these chronic toxicity studies are summarized in FIGURE 4. In the diagram, the daily doses are expressed as percentages of the acute oral lethal dose. With a daily oral administration of 300 mg./kg. phenylbutazone (23.4 per cent of the acute LD_{50}) over a period of 30 days, for example, 50 per cent of the animals died. Oxyphenbutazone shows a chronic toxicity of approximately the same order of magnitude as phenylbutazone. G 25671, on the other hand, is markedly less toxic: daily doses of 250 mg./kg. (55.6 per cent of the acute LD_{50}) resulted in a mortality of only 30 per cent. Sulfinpyrazone showed a surprisingly low toxicity in these tests: daily doses of 180 mg./kg. (48 per cent of the acute LD_{50}) caused no fatality during the test period of 30 days.

In interpreting these results, solubility, resorption, and biological half life of the compounds concerned must be taken into account. In the case of phenylbutazone and oxyphenbutazone, which differ in intravenous toxicity, mortality with oral administration seems to be determined by a very delayed resorption. The possibility of cumulative toxic action must be considered not only with oxyphenbutazone, which has a half life in rats of 8 hours,[27] but also with phenylbutazone, for which Burns *et al.*[7,8] have determined a half life in rats of 6 hours.

The extremely low chronic toxicity shown by sulfinpyrazone is particularly surprising in the light of the rapid intestinal absorption that this compound seems to undergo. For both G 25671 and sulfinpyrazone, Burns[9] indicated a biological half life in humans of 3 hours. In the case of the latter compound, the low chronic toxicity can certainly be ascribed to a rapid biotransformation by the rat, excluding the possibility of a cumulative toxic action.

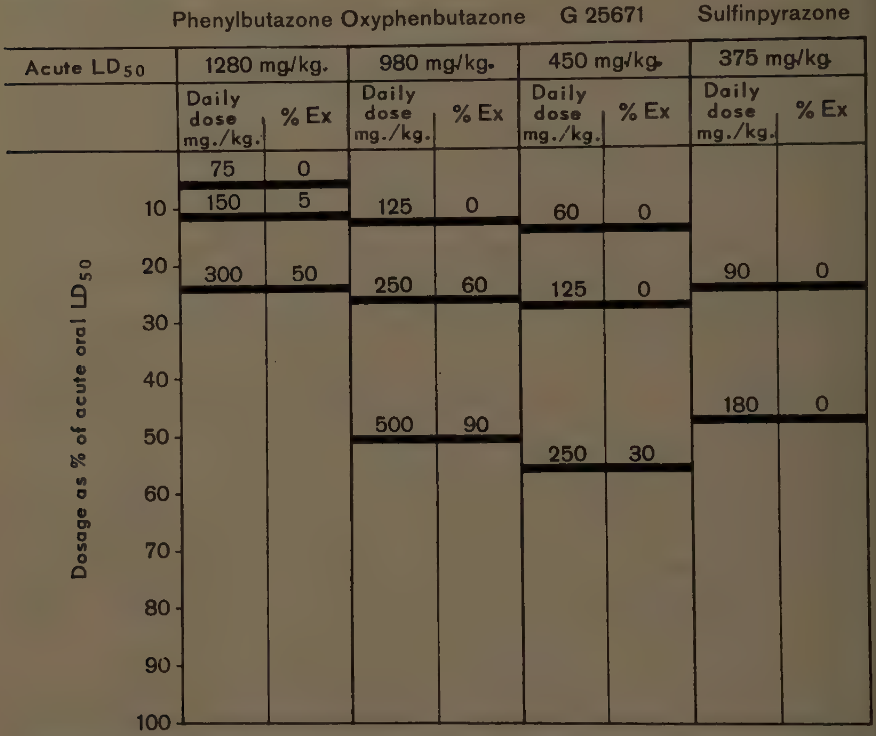

FIGURE 4. Subchronic toxicity in rats after daily intrastomachal administration for 30 days. Daily doses are given in mg./kg. and as percentages of acute oral LD_{50}. Lethality is expressed as percentage of fatalities among rats.

TABLE 3

PERCENTAGE FREQUENCY OF GASTRIC ULCERS IN THE RAT, 21 TO 22 HOURS AFTER SUBCUTANEOUS ADMINISTRATION

Dosage (mg./kg.)	Phenylbutazone	Oxyphenbutazone	G 25671	Sulfinpyrazone
2 × 50	10	0	40	10
2 × 75	62	8		
2 × 100	83		90	80
2 × 150	100		95	95
2 × 100			100	

Both in animals that died during the toxicity test and in those subsequently dissected, the following pathological changes in the region of the stomach and the upper small intestine were found fairly consistently: hyperemia of the stomach, petechial bleeding, and ulceration of the mucous membrane. Detailed studies of these pathological phenomenona have been made by Wilhelmi[63,64] and by Bonfils *et al.*[2] Wilhelmi[66] used the following method: the compound was administered subcutaneously in 2 doses 14 hours apart. The animals were sacrificed 21 to 22 hours after the first injection, and dissected. The usual number of animals used per dose was 50. The results are summarized in TABLE 3.

The results show that the ulcer-producing effects of G 25671 and of sulfinpyrazone are similar. There is a marked difference in this respect between oxyphenbutazone and phenylbutazone. Oxyphenbutazone, which could be given subcutaneously in doses only up to 75 mg./kg. on account of its high toxicity, caused mucosal ulceration at this dosage in only 4 of 50 animals. Hyperemia occurred in 30 of 50, inflammatory edema in 11 of 50 rats. The proportion of ulcerations with phenylbutazone at this dosage was 31 of 50 animals; hyperemia was found in 37 of 50, and edema in 28 of 50 animals. These figures indicate a distinctly better gastric tolerance for oxyphenbutazone, although this advantage is not apparent in the lethality during chronic administration. On the other hand, the low toxicities shown by sulfinpyrazone and G 25671 seem to exclude the possibility that the gastric lesions, which almost always occur, are the cause of death in chronic toxicity tests.

ANALGESIC PROPERTIES

The analgesic activity has been studied by Wilhelmi[66] in mice, rats, and rabbits, with use of the following methods:

(1) The pain threshold to electric stimulation of the dental pulp of the rabbit was determined by Gordonoff's method.[23] Special electrodes were inserted into the upper incisors, stimulation lasting for 1 sec. at a frequency of 50 cps. Four to 6 animals were used for each dose level, and tests were made with both intravenous and oral administration. The criterion of activity used was the increase in stimulation threshold as measured in volts; the values were given as percentages of the normal values. The results obtained are shown in TABLE 4.

(2) The reaction time following stimulation of the mouse tail by radiant light and heat was measured according to the method of Gross,[24] with the use of Friebel's apparatus.[22] The reaction time was measured in seconds and expressed as a percentage of the normal value. The maximum duration of stimulation was 20 sec.; 10 to 40 mice were used per dose. The results are given in TABLE 5.

(3) The increase in reaction time was measured by use of the "hot-plate" method of Woolfe and McDonald.[72] The temperature of the plate was 56° C., and the maximum stimulation time 25 sec. The results obtained are given in TABLE 6.

The results show that, of the pyrazoles tested, only aminopyrine possesses a distinct analgesic effect rendered apparent by all three test methods. The clinically well-known lower analgesic activity of phenylbutazone was detectable only by the method of Gordonoff and by the hot-plate procedure. With neither metabolite could an analgesic effect be demonstrated with certainty. On the rabbit tooth, G 25671 showed an analgesic effect of the same intensity as that of phenylbutazone; this derivative had no activity when tested by the other methods. These results show that biotransformation of phenylbutazone and G 25671 produces a loss of analgesic properties.

Wilhelmi[66] has made further studies to detect possible potentiating effects.

TABLE 4
ANALGESIC EFFECTS ON RABBITS*

	Administration	Dose (mg./kg.)	Elevation of stimulation threshold (%)
Phenylbutazone	I.V.	50	18
		75	40
		100	40
	Oral	600	23
Oxyphenbutazone	I.V.	20	5
		30	16
		50	—
G 25671	I.V.	50	15
		75	48 (toxic dose)
Sulfinpyrazone	I.V.	100	13
		150	25
Aminopyrine	I.V.	50	48 (convulsions in most cases)

* Electric stimulation of dental pulp.

TABLE 5
ANALGESIC EFFECTS ON MICE*

	Administration	Dose (mg./kg.)	Change in reaction time (%)
Phenylbutazone	I.P.	100	+6
		150	+23
	Oral	400	−1
Oxyphenbutazone	I.P.	50	+7 (effect partly lethal)
G 25671	I.P.	100	+6
		150	+11
Sulfinpyrazone	I.P.	100	+11
		150	+27
Aminopyrine	I.P.	50	+14
		75	+28
		100	+29
		150	+79

* Stimulation by radiant light and heat.

In contrast to phenylbutazone which, among other actions, increases the analgesic effect of morphine,[13,14,61] neither the metabolites nor G 25671 were found to possess such properties.

ANTIPYRETIC POTENCY

Antipyretic activity was studied by means of the so-called yeast fever of the rat. Six hours before the start of the test the animals received a subcutaneous injection of 10 ml./kg. of an emulsion of 15 per cent baker's yeast and 1 per cent tragacanth. Temperature was measured at intervals of 30 min. by thermal catheter and the effects were expressed as (1) the maximum fall in temperature in degrees Centigrade, and (2) the "hour-degree" integral expressing

TABLE 6
ANALGESIC EFFECTS ON MICE (HOT-PLATE METHOD)

	Administration	Dose (mg./kg.)	Increase in reaction time (%)
Phenylbutazone	I.P.	100	27
		150	57
	Oral	300	23
		400	28
Oxyphenbutazone	I.P.	25	13
		50	27 (slight stupor)
G 25671	I.P.	150	11
Sulfinpyrazone	I.P.	50	4
		100	13
		150	28
Aminopyrine	I.P.	50	26
		75	91
		100	141
		150	99

TABLE 7
ANTIPYRETIC EFFECT ON YEAST FEVER IN RATS

	Administration	Dose (mg./kg.)	Maximum antipyretic effect (°C.)
Phenylbutazone	I.P.	50	1.3
		100	2.1
		200	2.5
	Oral	100	1.3
Oxyphenbutazone	I.P.	50	1.1
		75	2.1
		100	3.3
	Oral	100	2.2
G 25671	I.P.	100	1.9
	Oral	100	1.4
Sulfinpyrazone	I.P.	100	0.0
	Oral	100	0.4
Aminopyrine	I.P.	50	2.0
		100	3.1
	Oral	100	2.0

both intensity and duration of effect. The compounds were administered intraperitoneally and orally, 6 animals being used per dose.

The antipyretic effects of the compounds tested are summarized in TABLE 7. The antipyretic action of phenylbutazone shows a clear correlation with the magnitude of dose; it does not attain the intensity of that of aminopyrine at the same dosage. The duration of the effect, which is of practical importance, cannot be adjudged with certainty by these experiments. As the antipyresis curves in FIGURE 5 show, the effect of phenylbutazone is maintained unchanged over the entire test period of 2½ hours. This long-lasting action can be ascribed in the main to the biological half life of 6 hours in the rat. The effect of aminopyrine is quite different: the maximum is reached 30 to 60 min. after intraperitoneal injection, but this effect drops off 60 to 90 min. after administration. These tests showed sulfinpyrazone to have no antipyretic potency. Its parent substance, G 25671, has an antipyretic action that is markedly superior to that of phenylbutazone. In regard to antipyretic potency, oxyphenbutazone is quite impressive: its antipyretic activity is equivalent in intensity and duration to that of aminopyrine.

EFFECTS ON RENAL FUNCTION

Detailed experimental studies of the effect of phenylbutazone on urate excretion have been made by Brodie, Yü, Burns, and their colleagues.[4,9,10,73] For the related derivatives, the intravenous doses, which have a clearly demonstrable uricosuric effect in gouty patients, are as follows: phenylbutazone, 800–1000 mg.; oxyphenbutazone 800–1000 mg.; G 25671 150–300 mg.; and sulfinpyrazone 30–70 mg.

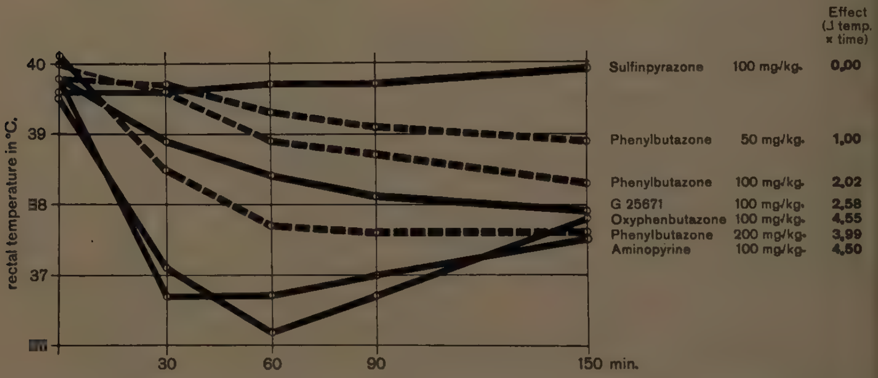

FIGURE 5. Antipyretic action on yeast fever of rats (intraperitoneal administration, average temperatures of 6 rats).

These observations were confirmed in clinical studies made by Kersley *et al.*[29] and Gutman and Yü,[26] which revealed that the intensity of the uricosuric effect of sulfinpyrazone was markedly superior to that of the most potent therapeutic agents used hitherto in gout.

During the investigation of some potentiator effects (morphine analgesia[13,14,61] persistence of *p*-aminosalicylic acid in blood,[42,43] and retardation of penicillin elimination[1]) Domenjoz and Eckel[14-17,20,21] observed a retarding effect of phenylbutazone on phenolsulfonphthalein excretion in rats. This activity, which is due to inhibition of tubular function, was reported for humans by Brodie *et al.*,[4] and sulfinpyrazone was observed by Burns *et al.*[9] to have a similar retarding effect in humans.

A comparative study on PSP-elimination has been made recently by my collaborator, Kreppel.[75] Anesthetized rats (60 mg./kg. Numal, I.P.) were given an intravenous dose of 75 mg./kg. of phenolsulfonphthalein. The compounds being investigated were administered simultaneously at a uniform dosage of 100 mg./kg., in identical injection volumes. The PSP level was determined in arterial blood samples 1, 2, and 3 hours after the injection of the dye.

The phenylbutazone analogues tested gave the blood levels shown in FIGURE 6.

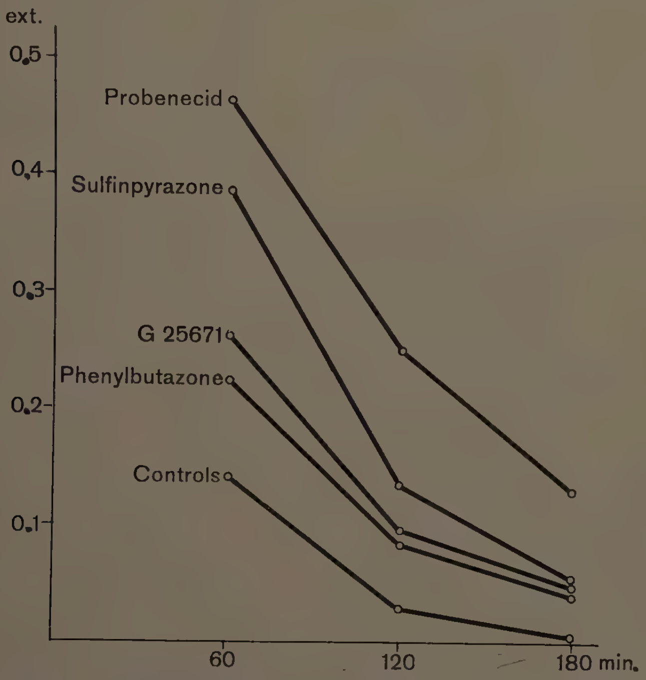

FIGURE 6. Phenolsulfonphthalein concentration in the blood of rats.

TABLE 8

RETARDATION OF PSP EXCRETION IN RATS

	Concentration of PSP in serum as per cent of concentration in controls	
	60 Min. after PSP injection	120 Min. after PSP injection
Phenylbutazone	156	282
G 25671	182	317
Sulfinpyrazone	271	462
Probenecid	327	862

Quantitative evaluation of the results yielded retardation effects for the first and second hours as shown in TABLE 8.

These data indicate that the effect of these analogues on PSP excretion in rats does not correspond entirely, either qualitatively or quantitatively, to the uricosuric activity measured in man. The extent to which the inhibition of tubular function, particularly by sulfinpyrazone, is of practical therapeutic mportance must remain the subject of further investigation.

Anti-inflammatory Activity

In view of the importance of this activity, a very detailed evaluation of anti-inflammatory properties was performed.

(1) In a preliminary routine investigation on formalin edema in rats, Wilhelmi[65,66] was able to show that oxyphenbutazone, G 25671, and sulfinpyrazone possess antiphlogistic properties similar to those of phenylbutazone. G 25671 appeared to have a somewhat stronger action in this respect.

Table 9

Inhibition of Formalin Edema in the Rat Following Oral Administration of Antiphlogistics

Doses (mg./kg.)	Animal weight (gm.)	No. of animals	Alteration of swelling (%)
Phenylbutazone			
200	154	20	−12
400	154	20	−19
600	154	19	−41
800	151	19	−57
Oxyphenbutazone			
100	159	19	+5
200	158	19	−10
400	160	19	−20
400	145	18	−23
600	146	9	−70
800	147	9	−55
G 25671			
100	146	19	+2
200	148	18	−5
400	153	20	−63
500	159	20	−34
Sulfinpyrazone			
50	162	20	−5
100	160	20	−13
200	164	20	−62
300	167	20	−92
Aminopyrine			
200	154	20	−31
400	160	20	−54
600	161	20	−55
800	159	19	−65

(2) A comparative and quantitative evaluation on formalin edema was performed by my collaborators Mörsdorf and Fehres (paper in preparation). Tests were made on groups of 20 rats with average weights of 150 gm. Formalin was injected subcutaneously in 3 per cent solution and in volumes of 0.1 ml.; the compounds concerned were administered orally in each case 60 min. before formalin. Tests were made with 4 or 5 different dose levels for each compound. The animals were sacrificed exactly 120 min. after the injection of formalin. The intensity of the edema was determined by comparison of the weights of the amputated feet with those of untreated animals. The results obtained are summarized in TABLE 9.

Comparative evaluation of the results by means of the graph in FIGURE 7 permits the following deductions:

Biotransformation of phenylbutazone yields a metabolite, oxyphenbutazone, that possesses an anti-inflammatory activity approximately equal to that of the parent compound, the degree of the inhibition of edema as well as the correlation between dose and effect being largely the same for both substances.

In this connection, the question arises as to what extent the anti-inflammatory effect of phenylbutazone may be due to the metabolite produced in the organism. In this regard, a study by Herrmann[27] dealing with the quantitative formation of oxyphenbutazone after administration of phenylbutazone is of interest. His results with rats, given in FIGURE 8, show that as soon as 1 to 2 hours after intravenous injection, a metabolite concentration in the blood of about half the phenylbutazone level is achieved. Corresponding studies with peroral administration have been carried out thus far only in rabbits. They show that the different rate of absorption results in a much slower rise in the blood levels of both phenylbutazone and oxyphenbutazone.

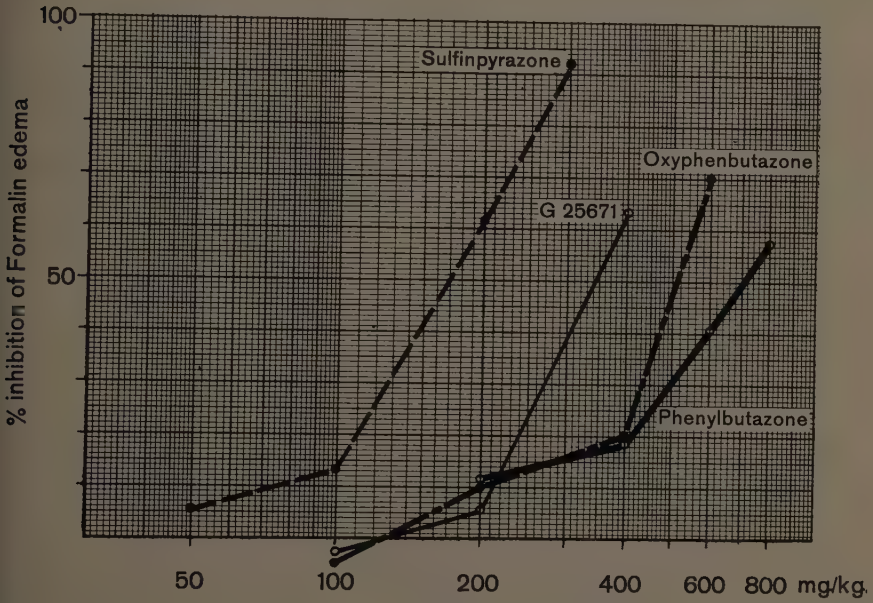

FIGURE 7. Inhibition of formalin edema in the rat (oral administration).

These findings suggest that part of the anti-inflammatory activity of phenylbutazone must be attributed to the presence of the metabolite. This question is not of great practical importance, however, since the parent substance and the metabolite have the same intensity of action.

The quantitative evaluation of G 25671 and its metabolite sulfinpyrazone is of particular interest since the latter possesses a much stronger anti-inflammatory potency than the parent compound. Sulfinpyrazone has about the same anti-inflammatory effect as G 25671 given in twice the dosage. Unfortunately, detailed investigations of blood levels in rats have not been made for these derivatives. In view of both the results obtained in the formalin-induced swelling and the known half life in man, sulfinpyrazone might be regarded as an important carrier of the anti-inflammatory action of G 25671. Obviously, we must take into consideration the fact that in our inflammation tests the oral route of administration provides particularly favorable conditions for sulfinpyrazone. It must be emphasized, however, that in formalin edema sulfinpyrazone orally administered gave really important inhibition values (92 per cent); these values were not approached even remotely by the other compounds (including phenylbutazone), even at the highest doses that can be tolerated.

(3) Serotonin edema in rats has been used by Theobald[54] to evaluate anti-inflammatory activity; swelling following subplantar injection of 50 γ serotonin in 1 ml. was measured, as we have described elsewhere.[56] Results were evaluated as indicated under (2). The active compounds were injected subcutaneously 30 min. prior to the serotonin injection. The method gave the results shown in TABLE 10.

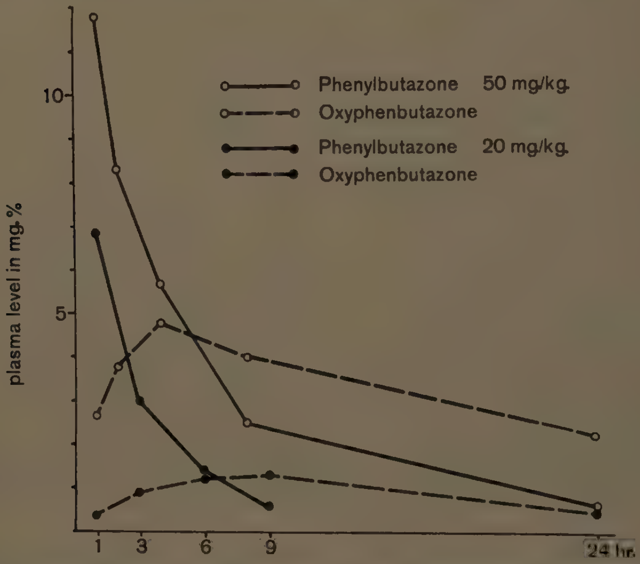

FIGURE 8. Plasma level of oxyphenbutazone after intravenous administration of phenylbutazone in the rat.

The diagram given in FIGURE 9 makes it clear that the effects of the compounds concerned on serotonin edema are different from the effects on formalin edema. Phenylbutazone and oxyphenbutazone are less effective on serotonin edema than on formalin swelling. Oxyphenbutazone inhibits serotonin edema in much smaller doses than does phenylbutazone. G 25671 is practically ineffective, while sulfinpyrazone exhibits a marked inhibitory action. Of interest is the comparison between aminopyrine and sodium salicylate: the former causes practically the same inhibition of serotonin edema at a subcutaneous dosage of 200 mg./kg. as does sodium salicylate at a level of 500 mg./kg. administered subcutaneously.

(4) In the evaluation of dextran swelling by Theobald,[54] 0.005 ml. of Macro-

dex (6 per cent sterile dextran solution) was injected subcutaneously. Time intervals were as in serotonin edema, and the results were evaluated as explained under (2).

The investigation of edema inhibition by means of dextran swelling is partic-

TABLE 10

ALTERATION IN PERCENTAGE OF SEROTONIN AND DEXTRAN EDEMA IN THE RAT FOLLOWING SUBCUTANEOUS ADMINISTRATION OF ANTIPHLOGISTICS

	Dosage (mg./kg.)	Serotonin edema	Dextran edema
Phenylbutazone	100	+6	−21
	200	−27	−26
Oxyphenbutazone	75	+8	−19
	100	−30	−12
G 25671	200	−13	−23
	300	−15	−46
Sulfinpyrazone	100	+6	−27
	200	−38	−59
Aminopyrine	100	0	−36
	200	−58	−74
Na salicylate	200	0	−27
	500	−54	−77

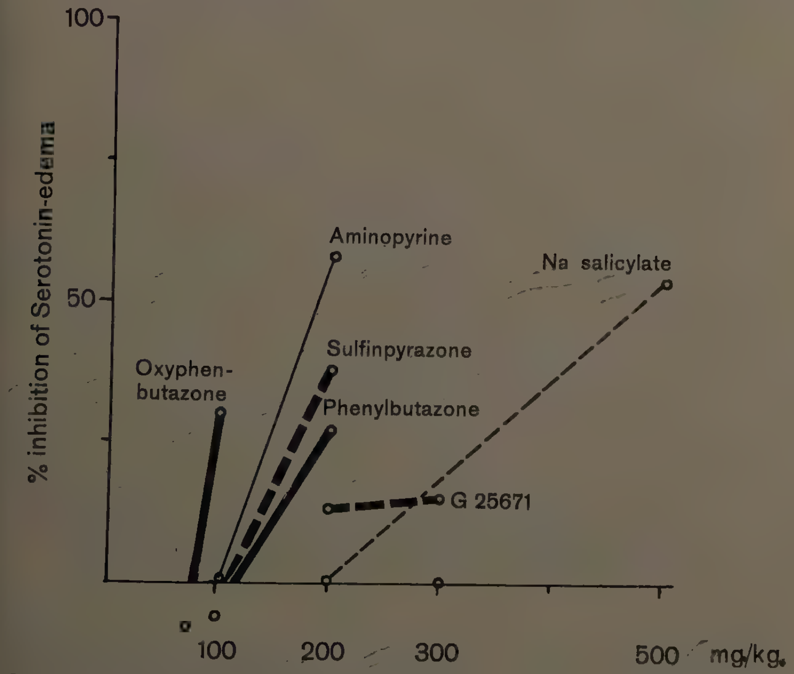

FIGURE 9. Inhibition of serotonin edema in the rat (subcutaneous administration).

ularly interesting on account of the allergic character of this reaction. In assessing the results, however, it must not be forgotten that, in addition to the local reaction, general toxic effects arise due to the resorption of dextran. Phenylbutazone is only slightly effective against dextran edema, and its metabolite oxyphenbutazone is practically ineffective (TABLE 10). These observations demonstrate that the mechanisms involved in dextran swelling are different from those responsible for formalin edema.

Both sulfinpyrazone and G 25671 have a characteristic inhibitory action on dextran edema. Their antiphlogistic mechanisms are therefore probably different from those of phenylbutazone and oxyphenbutazone. Sulfinpyrazone shows a markedly stronger activity than G 25671.

Since both serotonin and histamine must be considered as mediators of dextran edema, it was of interest to investigate the histamine-antagonistic properties of the phenylbutazone analogues concerned. Some years ago specific antihistaminic effects of the pyrazoles were demonstrated in the isolated rabbit ear.[13,14,28] This effect must be attributed to a direct action on the smooth muscles of the vessels; it cannot be demonstrated on isolated intestines.

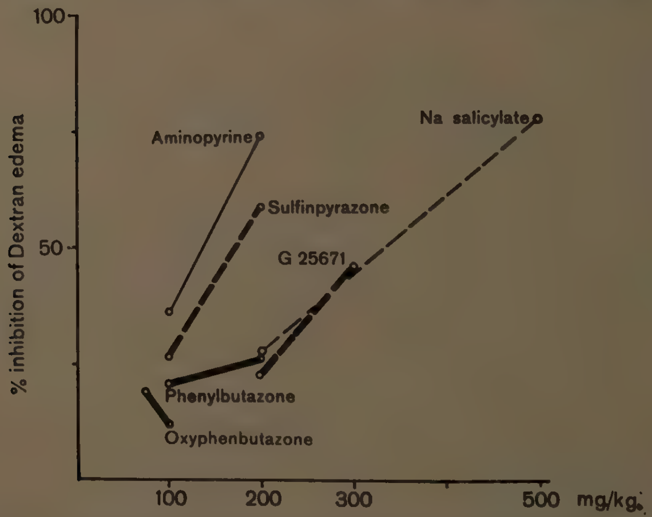

FIGURE 10. Inhibition of dextran edema in the rat (subcutaneous administration).

The tests were carried out in the usual manner, the technique of Krawkow-Pissemski[31,37,38] involving perfusion with Tyrode's solution being used. The compounds being tested were injected in equal volumes into the perfusion circuit. The amount of fluid emerging from the vein of the ear was recorded by a drop counter (measuring the interval between successive drops) in connection with the ordinate recorder of Fleisch. The compound *N*-benzyl-*N*,*N*′-dimethyl-*N*-*p*-phenylethylenediamine (Antergan) was used as standard.

FIGURE 11*a*, *b*, *c*, and *d* show the effects observed with this method. Quantitative evaluation of the histamine-antagonistic activity (TABLE 11) indicates that aminopyrine possesses the strongest action. In order of decreasing potency come phenylbutazone, oxyphenbutazone, G 25671 and, finally, the only

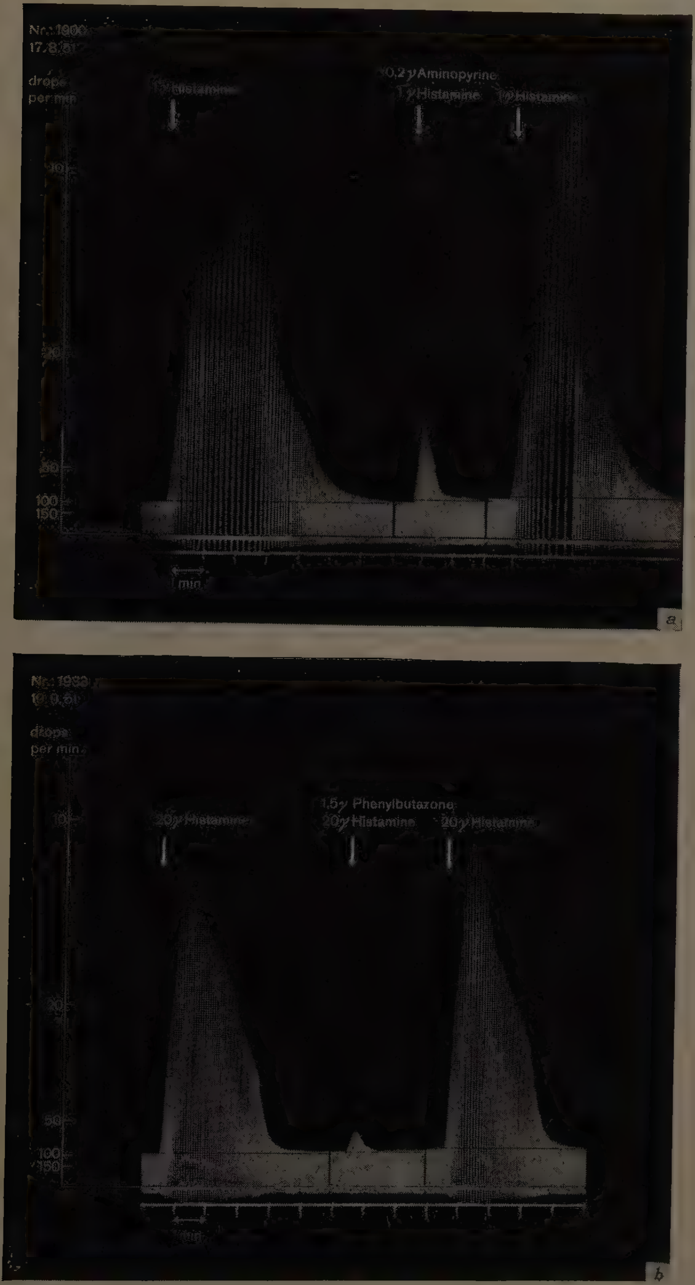

Figure 11*a* and *b*. Antihistaminic effect on the isolated rabbit's ear.

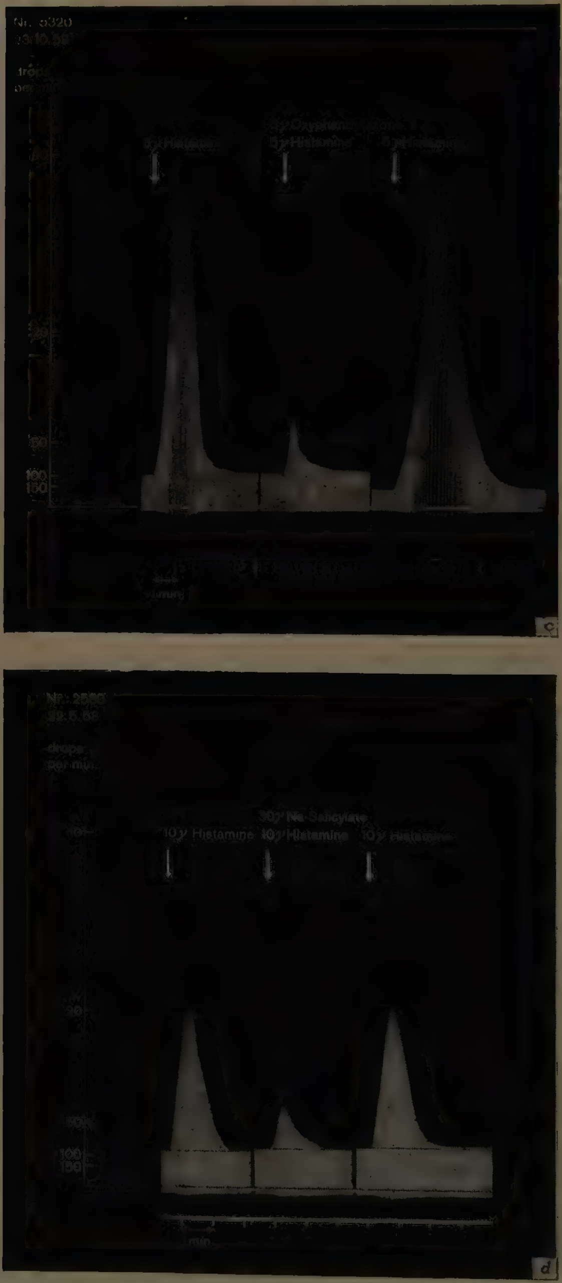

FIGURE 11*c* and *d*. Antihistaminic effect on the isolated rabbit's ear.

slightly effective sulfinpyrazone. FIGURE 11 shows that Na salicylate too has very distinct antihistaminic activity. No correlation of these results with the intensity of the anti-inflammatory effect on dextran edema is apparent.

(5) In Wilhelmi's comparative investigation[66] using the granuloma pouch

TABLE 11
ANTIHISTAMINIC EFFECTS ON THE PERFUSED RABBIT EAR

	Amount equivalent to 1 γ BDP*	Minimum effective dose (γ)
Phenylbutazone	14	1.5
Oxyphenbutazone	100	1.0
G 25671	120	1.5
Sulfinpyrazone	1350	30.0
Aminopyrine	4.1	0.2
Sodium salicylate	225	2.0

* BDP = *N*-benzyl-*N*,*N'*-dimethyl-*N*-phenylethylenediamine (Antergan).

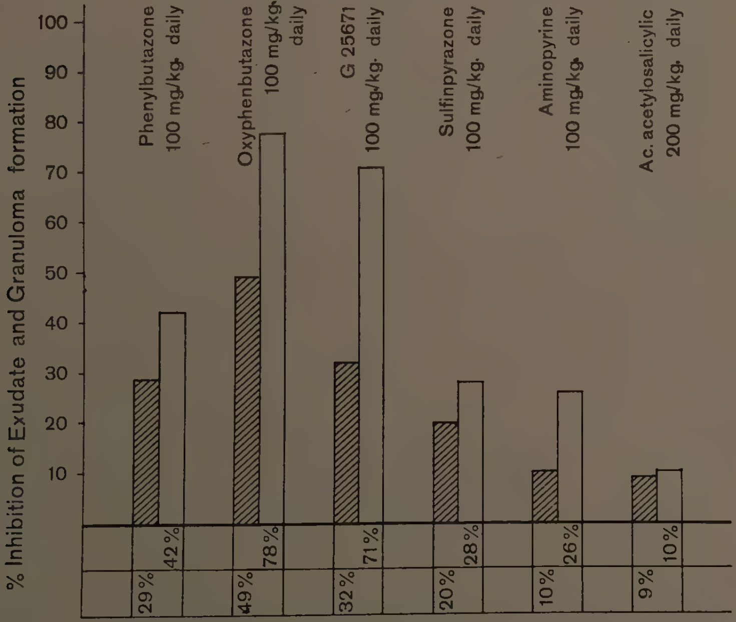

FIGURE 12. Antiphlogistic activity in the granuloma pouch of the rat (oral administration over 14 days). Cross-hatched areas, granuloma formation; light areas, exudate.

technique of Selye,[50] phenylbutazone and G 25671 and their metabolites showed an anti-inflammatory activity that was markedly superior to that of aminopyrine and of sodium salicylate given at the same dose level (FIGURE 12). In this test, oxyphenbutazone was distinctly more active than phenylbutazone. Sulfinpyrazone was somewhat weaker than phenylbutazone, but still more active than aminopyrine.

The granuloma pouch was produced in rats by injection of 25 ml. of air plus

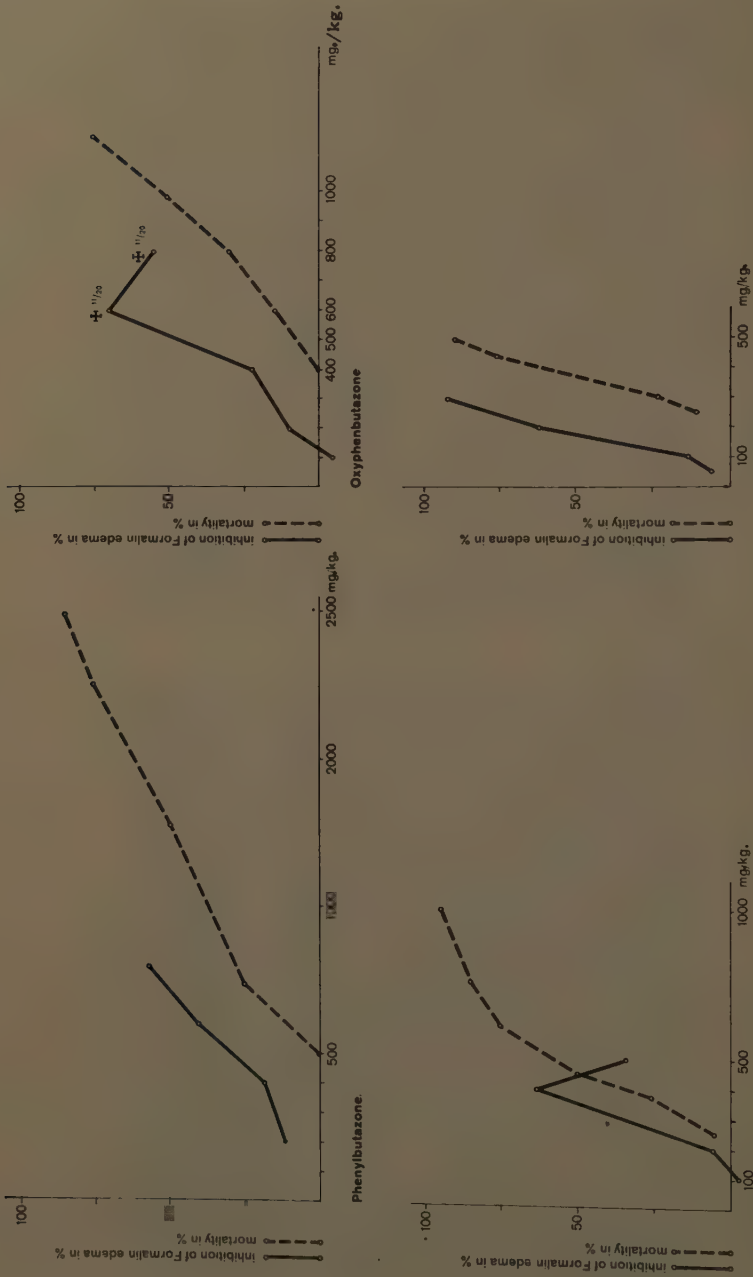

FIGURE 13. Inhibition of formalin edema and lethality in the rat (oral administration).

ml. of 1 per cent croton oil in bone oil. The compounds to be tested were iven orally once daily on 14 successive days. On the fourteenth day, the ani- nals were sacrificed. The amount of the hemorrhagic exudate and the weight f the empty granuloma pouch were measured. The protein content of the xudate was determined by the method of Esbach. The results were related o control values in untreated animals and expressed as percentage inhibitions.

(6) Tests with formalin peritonitis, described by Wilhelmi,[65,66] also indicated hat phenylbutazone and G 25671 and their derivatives possess marked anti- nflammatory activity. Subcutaneous doses of 150 mg./kg. of phenylbutazone, G 25671, and sulfinpyrazone resulted in almost identical inhibition values of 7, 48, and 48 per cent. On account of its toxicity, oxyphenbutazone could be iven only in low dosage, and hence it showed a correspondingly low activity. Comparative evaluation yielded the interesting fact that 250 mg./kg. of ace- ylsalicylic acid caused 63 per cent inhibition in exudate formation.

TABLE 12

	Amount causing 50% inhibition of edema (mg./kg.)	Lethality (%)
G 25671	ca. 360	ca. 23
Phenylbutazone	ca. 710	ca. 23
Oxyphenbutazone	ca. 520	ca. 8
Sulfinpyrazone	ca. 180	0

(7) Evaluation made by Wilhelmi[65,66] with ultraviolet erythema in guinea igs showed oxyphenbutazone to be completely inactive. For the remaining ompounds, the minimum doses effecting 50 per cent inhibition, were as follows:

Phenylbutazone	S.C.	ca. 11.25 mg./kg.
G 25671	S.C.	ca. 14.5 mg./kg.
Sulfinpyrazone	S.C.	ca. 50.0 mg./kg.

Objection frequently is made to anti-inflammatory evaluation by animal ex- eriments, for the reason that these results are obtained with doses far above erapeutic levels. In order to counter this objection, I have compared the ndings of my collaborators Mörsdorf and Fehres (paper in preparation) on for- alin edema with lethality curves obtained by administering the compounds the same way to animals of the same species. The graphs in FIGURE 13 ow, in fact, that in the cases of G 25671, phenylbutazone, and oxyphenbuta- ne, the doses at which the compounds manifest anti-inflammatory properties early lie in part in the toxic region. Lethality values and values obtained by terpolation for doses causing 50 per cent inhibition of inflammatory edema e given in TABLE 12.

I emphasize that these results were obtained in rats with respect to a spe- ic inflammation model and under peroral administration; they do not permit y generalization to other modes of administration or other species. This mparison of anti-inflammatory activity with toxicity shows, however, that yphenbutazone and especially sulfinpyrazone are endowed with exceptional ti-inflammatory activities.

In order to explain the mechanism of action of these drugs, in particular that of phenylbutazone, we have drawn attention in earlier papers[13-16,18,19,52,55] to the following special properties of this compound.

(1) Phenylbutazone, like almost all pharmacologically active substances, exhibits adrenotropic effects that are detectable as ascorbic acid- and cholesterol-depletion of the adrenals. These adrenotropic effects disappear after hypophysectomy. Their significance with regard to the pharmacological and therapeutic actions of phenylbutazone is not clear.

(2) The anti-inflammatory properties of phenylbutazone demonstrated in experimental inflammation differ both in quantity and in quality from the antiphlogistic effects of the salicylates and steroids. The anti-inflammatory activities of pyrazolidine derivatives, in particular that of phenylbutazone, are not distinctly affected by hypophysectomy; they thus bear no relationship to the component responsible for adrenal depletion. We observed in earlier studies on anesthetized animals that, as a consequence of adrenalectomy, antiphlogistic activity of all pyrazole compounds tested was reduced in a certain degree but not abolished. The loss amounted to about 30 per cent with phenylbutazone and 80 per cent with aminopyrine.

TABLE 13

PERCENTAGE INHIBITION OF FORMALIN EDEMA IN NORMAL, HYPOPHYSECTOMIZED, AND ADRENALECTOMIZED RATS, FOLLOWING SUBCUTANEOUS ADMINISTRATION OF ANTIPHLOGISTICS

	Doses (mg./kg.)	Normal animals	Hypophysectomized animals	Adrenalectomized animals
Phenylbutazone	150	51	60	51
Oxyphenbutazone	75	27	54	28
G 25671	150	40	43	19
Sulfinpyrazone	150	59	65	37
	100	35	56	35
Aminopyrine	150	50	68	25
Na salicylate	250	23	56	26
	350	35	54	12
Acetylsalicylic acid	350	35	63	29

(3) Our results incline us to the view that the anti-inflammatory activity of phenylbutazone must be attributed to a peripheral component active in the inflamed area. In support of this are (a) the results of tests with local application,[62,71] and (b) the high tissue concentration, for example, storage of these compounds in inflamed tissues demonstrated by Wilhelmi *et al.*[70]

My collaborators Mörsdorf and Fehres have recently studied the anti-inflammatory activity of several compounds on formalin edema in unanesthetized normal, hypophysectomized, and adrenalectomized rats (to be published). In order to ensure that the results would be comparable, animals of a single strain were used in all the tests. The compounds were administered subcutaneously 30 min. prior to formalin injection. Hypophysectomy and adrenalectomy were carried out under ether 40 to 50 hours before the inflammation test. The success of hypophysectomy was confirmed by dissection. Evaluation of the results was made as explained under (2) (see TABLE 13). A comparative assessment is shown graphically in FIGURE 14.

It is apparent that the activity of phenylbutazone is not reduced by either ypophysectomy or adrenalectomy. Aminopyrine was observed to cause a 50 er cent reduction in antiphlogistic activity following adrenalectomy; this coresponds to earlier findings in anesthetized rats. Of the remaining pyrazole erivatives, G 25671 exhibited behavior similar to that of aminopyrine. Adenalectomy did not affect the activity of oxyphenbutazone or sulfinpyrazone hen the latter was administered in low dosage. Further experiments are reuired to confirm the observation that, with some compounds, hypophysectomy s followed by a marked increase in activity. No explanation of this phenomnon is possible at present.

The comparison with sodium salicylate and acetylsalicylic acid is of interest. n our tests subcutaneous dosages of 350 mg./kg. of acetylsalicylic acid, had imilar anti-inflammatory potencies in both normal and adrenalectomized nimals. Identical effects were also observed in normal and adrenalectomized nimals given 250 mg./kg. sodium salicylate. In a further test series with odium salicylate at a subcutaneous dose of 350 mg./kg., a 60 per cent reducion of antiphlogistic activity followed adrenalectomy. In my opinion, it is ot justifiable to consider this latter result as proof of an adrenal mode of action. xamination of the animals that received this dose revealed symptoms of genral intoxication. In fact, of the 31 adrenalectomized rats tested, 14 or 45 per ent of them died. In my view, the results obtained with sodium salicylate nd acetylsalicylic acid at subcutaneous doses of 250 mg./kg. disprove the eory of an adrenal mode of action of salicylates as put forward by Roskam nd Van Cauwenberge[44-47] and others.

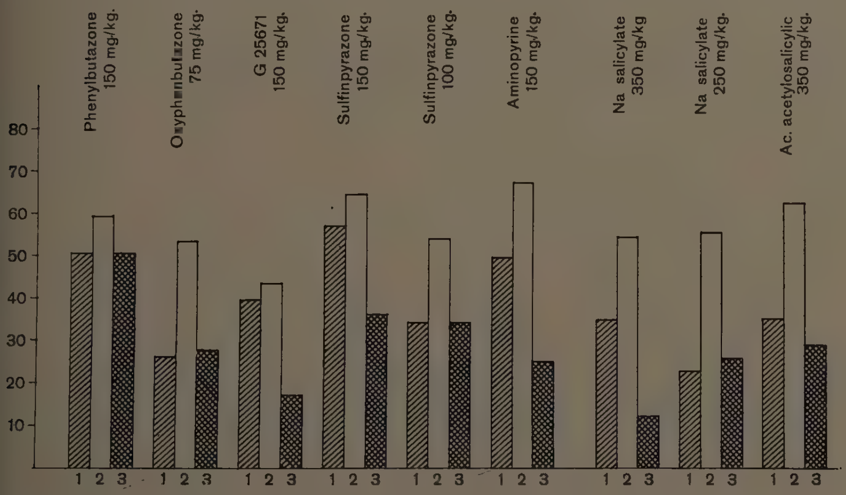

FIGURE 14. Inhibition of formalin edema in rats; subcutaneous administration to 1, noral animals; 2, hypophysectomized animals; 3, adrenalectomized animals.

The local action of phenylbutazone analogues has been examined by my ollaborator Mörsdorf[34] (and to be published), who used a common dye technique. vans' blue was administered intravenously to rats in a 2 per cent solution. n one of the hind paws, dextran edema was produced by subcutaneous injecon of 150 γ of dextran in 0.1 ml. physiological saline. The other hind paw received a simultaneous injection of 150 γ dextran plus 150 γ of the compound tested, in 0.1 ml. saline. The extent to which extravasation of the dye occurred was recorded 3, 10, and 30 min. after the injection of dextran.

The results are shown graphically in FIGURE 15. It will be noted that with every compound tested there was more or less marked inhibition of extravasation. With certain limitations this result can be regarded as indicating a loca blockade, that is, the existence in the group of pyrazolidines of a periphera component that may be of importance also in connection with inhibition of inflammation.

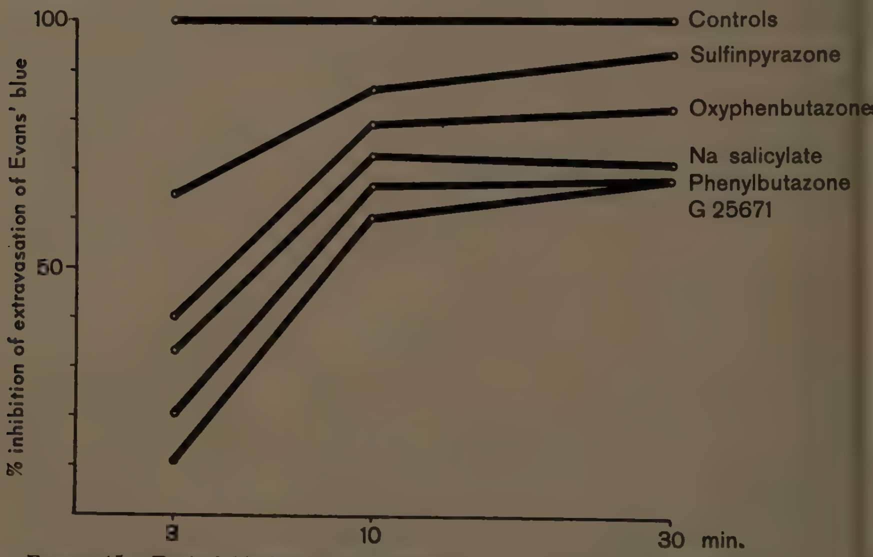

FIGURE 15. Topical blockade resp. retardation of Evans' blue extravasation into the area of dextran injection in the rat. Control paw: 150 γ dextran in 0.1 ml.; test paw: 150 γ dextran + 150 γ of each drug in 0.1 ml.

CONCLUSIONS

The metabolic breakdown of phenylbutazone gives rise to a metabolite, oxyphenbutazone, to which a part of the activity of the parent compound must be ascribed. From the toxicological point of view, oxyphenbutazone is distinctly more active than its precursor. Judged by the median lethal dose under intravenous administration, oxyphenbutazone is at least twice as active, that is, twice as toxic, as phenylbutazone. With oral administration, the median lethal doses of oxyphenbutazone are about 30 per cent lower than those of phenylbutazone. These figures make it likely that intestinal absorption of oxyphenbutazone is slower than that of phenylbutazone. This fact can explain why oxyphenbutazone, under conditions of chronic administration, has roughly the same effect as phenylbutazone, in spite of its higher acute toxicity.

Oxyphenbutazone has a markedly weaker ulcerogenic effect on the gastric mucosa than has phenylbutazone. This fact is of practical interest because it denotes a better gastric tolerance, at least for the rat.

Analgesic activity has not been demonstrated with certainty for oxyphenbutazone. On the other hand, its antipyretic potency is markedly stronger than that of phenylbutazone: its effect on yeast fever in rats is equivalent to that of aminopyrine.

Evaluation of the anti-inflammatory activity of formalin edema shows that quantitatively oxyphenbutazone and phenylbutazone have identical potencies. The actions on serotonin-induced swelling, on dextran edema, on UV erythema, and on formalin peritonitis indicate that the antiphlogistic mechanisms of oxyphenbutazone are different from those of phenylbutazone. It is of interest to note that oxyphenbutazone, when tested by the granuloma-pouch method under conditions of chronic administration, causes a markedly stronger inhibition of granuloma- and exudate-formation than does phenylbutazone.

We know less about the adequacy of our inflammatory tests and clinical conditions, but we can deduce from the reported results that the therapeutic applications of oxyphenbutazone may be different from those of phenylbutazone. In the case of pain conditions, the lack of an analgesic component may be a disadvantage. As an antipyretic agent, oxyphenbutazone should be superior to phenylbutazone.

The biotransformation of G 25671 into sulfinpyrazone results in a distinct change in quantitative and qualitative properties. With respect to acute toxicity, the metabolite sulfinpyrazone, when given intravenously to mice and rabbits, is slightly less toxic than its precursor. In mice, at least, oral administration of sulfinpyrazone has markedly more toxic effects than G 25671; this result indicates a more favorable intestinal absorption. In spite of the identical half lives of these substances in man, the tolerance of rats for chronic doses of sulfinpyrazone is better than that for G 25671. In chronic toxicity tests over a period of 30 days, daily doses of 50 per cent of the oral acute lethal dose were tolerated without injury by all the test animals.

When given in the same dosage, sulfinpyrazone had about the same effect as G 25671 or phenylbutazone as regards ulceration of the gastric mucosa of the rat.

There were only slight indications of an analgesic activity in sulfinpyrazone, and there was no evidence at all for an antipyretic component. The loss of these components, which are concerned with central nervous functions and are characteristic for the pyrazoles, is possibly a reflection of the particular solubility relationships and the low pK_a value of sulfinpyrazone.

In the phenolsulfonphthalein test, sulfinpyrazone had a stronger effect on tubular function than any other of the compounds tested. However, in this respect sulfinpyrazone did not attain the potency of equal doses of probenecid.

In regard to the anti-inflammatory activity spectrum, it is of the greatest interest to note that sulfinpyrazone has a markedly stronger effect on formalin edema and on dextran swelling than its parent substance or phenylbutazone. It is noteworthy that, in the case of formalin edema, the maximal inhibition values reached with sulfinpyrazone (92 per cent) were not even approached by any other pyrazole derivative. At the same time it should be emphasized that, with sulfinpyrazone, the relationship between the antiphlogistically effective doses and the toxic doses is a particularly favorable one. This compound, even in dosages corresponding to zero lethality under conditions of oral intake, appeared to effect 50 per cent inhibition of inflammation, a situation without parallel so far as the other derivatives are concerned.

This last peculiarity might be of particular importance for the clinical application of sulfinpyrazone. The half life of 3 hours in man[9] makes it necessary to administer it in 4 to 5 individual doses over a 24-hour period, a regime which should ensure favorable conditions for its anti-inflammatory potency in the human. The antiphlogistic activity of sulfinpyrazone is of importance too in view of its present predominant use as an uricosuric agent. Many clinical forms of gout are marked by local inflammatory reactions around the tophi and by painful attacks which are the result of inflammatory processes. The objectively and subjectively favorable effects of sulfinpyrazone in gout are to be attributed to an optimal combination of uricosuric and anti-inflammatory properties. Extensive clinical studies are necessary to decide whether sulfinpyrazone is also suitable for the treatment of rheumatic and other inflammatory conditions. Such studies obviously must take into account the rapid biotransformation of this compound.

ACKNOWLEDGMENTS

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REFERENCES

1. BOECKH, P. 1952. Therap. Umschau. **9:** 93.
2. BONFILS, S., J. P. HARDUIN & M. BOUREL. 1953. Production of gastric ulcer in rats by ingestion of phenylbutazone. Compt. rend. soc. biol. **147:** 2016.
3. BRODIE, B. B., E. W. LOWMAN, J. J. BURNS, P. R. LEE, T. CHENKIN, A. GOLDMAN, M. WEINER & J. M. STEELE. 1954. Observations on the antirheumatic and physiologic effects of phenylbutazone (Butazolidin) and some comparisons with cortisone. Am. J. Med. **16:** 181.
4. BRODIE, B. B., T. F. YÜ, J. J. BURNS, T. CHENKIN, B. C. PATON, J. M. STEELE & A. B. GUTMAN. 1954. Observations on G 25671, a phenylbutazone analogue (. . .). Proc. Soc. Exptl. Biol. Med. **86:** 884.
5. BURNS, J. J., A. SCHULERT, T. CHENKIN, A. GOLDMAN & B. B. BRODIE. 1952. The physiological disposition of phenylbutazone (Butazolidin), a new antirheumatic agent. J. Pharmacol. Exptl. Therap. **106:** 375.
6. BURNS, J. J., R. K. ROSE, T. CHENKIN, A. GOLDMAN, A. SCHULERT & B. B. BRODIE. 1953. The physiological disposition of phenylbutazone (Butazolidin) in man and a method for its estimation in biological material. J. Pharmacol. Exptl. Therap. **109:** 346.
7. BURNS, J. J., R. K. ROSE, S. GOODWIN, J. REICHENTHAL, E. C. HORNING & B. B. BRODIE. 1955. The metabolic fate of phenylbutazone (Butazolidin) in man. J. Pharmacol. Exptl. Therap. **113:** 481.
8. BURNS, J. J., R. K. ROSE, S. GOODWIN, J. REICHENTHAL, E. HORNING & B. B. BRODIE. 1955. Studies on the biotransformation of phenylbutazone (Butzolidin). J. Pharmacol. Exptl. Therap. **113:** 9.
9. BURNS, J. J., T. F. YÜ, A. RITTERBRAND, J. M. PEREL, A. B. GUTMAN & B. B. BRODIE. 1957. A potent new uricosuric agent, the sulfoxide metabolite of the phenylbutazone analogue, G 25671. J. Pharmacol. Exptl. Therap. **119:** 418.
10. BURNS, J. J., T. F. YÜ, P. DAYTON, L. BERGER, A. B. GUTMAN & B. B. BRODIE. 1958. Relationship between pK_a and uricosuric activity in phenylbutazone analogues. Nature. **182:** 1162.
11. CONNELL, J. F. & L. M. ROUSSELOT. 1959. The clinical evaluation of a new anti-inflammatory agent. Am. J. Surg. **98:** 31.

12. Domenjoz, R. 1952. Pharmacological aspects of phenylbutazone (Butazolidin T. M.), a new antirheumatic. Federation Proc. **11:** 339.
13. Domenjoz, R. 1952. Some pharmacological aspects of phenylbutazone (Butazolidin T. M.), a new antirheumatic. Intern. Record. Med. Gen. Prac. Clin. **165:** 467.
14. Domenjoz, R. 1953. Pharmacological evaluation of anti-inflammatory agents, a contribution to the pharmacology of phenylbutazone (Butazolidin T.M.). Ann. Univ. Saraviensis Med. **1:** 317.
15. Domenjoz, R. 1954. Sur le mécanisme d'action des substances anti-inflammatoire. R. Hazard: Actualités Pharmacologiques. Serie VII. 73. Masson. Paris, France.
16. Domenjoz, R. 1955. Pharmakotherapeutische Weiterentwicklung der Antipyretica-Antalgetica. Arch. exptl. Pathol. Pharmakol. **225:** 14.
17. Domenjoz, R., H. Eckel & W. Theobald. 1955. Zur Untersuchung der sogenannten Synovialpermeabilität. Monatsschr. Psychiat. Neurol. **129:** 29. (Festschrift Grünthal.)
18. Domenjoz, R., K. Mörsdorf & E. G. Stenger. 1956. Zur Frage verschiedener adrenotroper Mediatoren bei Auslösung der Nebennieren-Depletion an Ascorbinsäure und Cholesterin. Arzneimittel-Forsch. **6:** 591.
19. Domenjoz, R., W. Theobald, E. G. Stenger & K. Mörsdorf. 1955. Die Wirkung der Antiphlogistica auf das Formalinoedem, den Ascorbinsäure- und den Cholesteringehalt der Nebenniere an der hypophysenlosen Ratte. Arch. intern. pharmacodynamie. **103:** 341.
20. Eckel, H. 1955. Der Einfluss von Retardmitteln und von entzündungshemmenden Pharmaka auf den Phenolsulfonphthalein-Blutspiegel der Ratte. Ann. Univ. Saraviensis Med. **3:** 11.
21. Eckel, H. & W. Theobald. 1955. Die Wirkung von Retardmitteln auf den Phenolsulfonphthaleinblutspiegel bei der Ratte. Arch. exptl. Pathol. Pharmakol. **225:** 184.
22. Friebel, H. & C. Reichle. 1955. Zur analgetischen und analgesieverstärkenden Wirkung von Chlorpromazin (Megaphen). Arch. exptl. Pathol. Pharmacol. **226:** 551.
23. Gordonoff, T. 1958. Therap. Umschau. **15:** 331.
23*a*. *vide* Batt, U. 1935. Dissertation. Bern, Switzerland.
23*b*. *vide* Ruckstuhl, K. 1939. Dissertation. Bern, Switzerland.
24. Gross, F. 1947. Eine einfache Methode zur quantitativen Analgesieprüfung. Helv. Physiol. et Pharmacol. Acta. **5:** C 31.
25. Gsell, O. & W. Müller. 1950. Parenterale Pyramidon-Pyrazolidin-Therapie von Rheumatismus und Infektionen mittels Irgapyrin. Schweiz. med. Wochschr. **80:** 310.
26. Gutman, A. B. & T. F. Yü. 1957. Protracted uricosuric therapy in tophaceous gout. Lancet. **1:** 1258.
27. Herrmann, B. 1959. Über den Stoffwechsel des Butazolidin. Medicina Experimentalis. **1:** 170.
28. Jaques, R. & R. Domenjoz. 1950. Histaminantagonistische Wirkung bei Pyrazolen und Antihistaminen. Arch. exptl. Pathol. Pharmakol. **212:** 124.
29. Kersley, G. D., E. R. Cook & D. C. J. Tovey. 1958. Value of uricosuric agents and in particular of G 28315 in gout. Ann. Rheumatic Diseases. **17:** 326.
30. Knorr, L. 1884. Einwirkung von Acetessigester auf Hydrazinchinizidinderivate. Ber. deut. chem. Ges. **17:** 546.
31. Krawkow-Pissemski. *vide:* Pissemski.
32. Kuipers, R. K. W. & C. Tazelaar-Onderwater. 1956. Experiences with the new pyrazolone-derivate G 25671. Contemporary Rheumatol. **:** 525.
33. Mason, R. M. & F. Cramer. 1951. Phenylbutazone and its derivatives. Brit. Med. J. **:** 1351.
34. Mörsdorf, K. & L. Fehres. 1959. 5-Hydroxytryptamin (5-HT) und hyperergische Reaktion. Medicina Experimentalis. **1:** 58.
35. O'Reilly, T. J. 1958. A new antirheumatic drug (G 27202 Geigy). J. Irish Med. Assoc. **43:** 217.
36. Paton, B. C., B. B. Brodie, T. F. Yü, J. J. Burns, T. Chenkin, J. M. Steele & A. B. Gutman. 1955. Observations on G 25671, a phenylbutazone analogue (. . .). J. Pharmacol. Exptl. Therap. **113:** 42.
37. Pissemski, S. A. 1914. Über den Einfluss der Temperatur auf die peripheren Gefässe. Pflüger's Arch. ges. Physiol. **156:** 426.
38. Pissemski, S. A. 1914. Pflüger's Arch. ges. Physiol. **157:** 501.
39. Pulver, R. 1950. Über Irgapyrin, ein neues Antirheumaticum und Analgeticum. Schweiz. med. Wochschr. **80:** 308.
40. Pulver, R. Intern. Rept. I. R. Geigy Ltd. Basel, Switzerland.
41. Pulver, R., B. Exer & B. Herrmann. 1956. Über die Beeinflussung enzymatischer Reaktionen durch Phenylbutazon und die Übertragbarkeit fermentchemischer Befunde auf die Stoffwechselprozesse der Zelle. Schweiz. med. Wochschr. **86:** 1080.

42. Pulver, R. & G. Wilhelmi. 1952. Über den Einfluss von Pyrazolen, insbesondere Irgapyrin, auf die Blutkonzentration der p-Aminosalicylsäure (Retardwirkung). Schweiz. Z. Tuberk. **9:** 86.
43. Regli, J. & R. Pulver. 1952. Über Irgapyrin als Retardmittel. Schweiz. Z. Tuberk. **9:** 312.
44. Roskam, J. 1956. Les modes d'action direct et indirect de la salicylothérapie. Semaine hôp. Paris. **32:** 291.
45. Roskam, J. 1956. Que peut-on objecter au concept: "Salicylothérapie médication hormonopoiétique?". Bull. acad. suisse sci. méd. **12:** 120.
46. Roskam, J. & H. Van Cauwenberge. 1952. Cortisone, ACTH et salicylés dans le traitement des rhumatismes inflammatoires et des états similaires. Presse méd. **60:** 1344.
47. Roskam, J. & H. Van Cauwenberge. 1954. Comment agissent les salicylés? Comment faut-il les prescrire? Presse méd. **62:** 165.
48. Schottmüller, H. 1927. Behandlung des akuten und chronischen Gelenkrheumatismus mit Pyramidon. Münch. med. Wochschr. **74:** 861.
49. Schottmüller, H. 1929. Über akute Gelenkentzündungen, ihre Aetiologie und Behandlung. Münch. med. Wochschr. **76:** 445, 499.
50. Selye, H. 1953. Use of "granuloma-pouch" technic in the study of antiphlogistic corticoids. Proc. Soc. Exptl. Biol. Med. **82:** 328.
51. Serre, H., L. Simon, M. Delange & M. J. Claustre. 1959. Action thérapeutique de l'uricosurique G 28315. Presse méd. **67:** 1165.
52. Stenger, E. G., K. Mörsdorf & R. Domenjoz. 1955. Die Bedeutung der Ascorbinsäure und Cholesterindepletion für die Beurteilung des Wirkungsmechanismus entzündungshemmender Substanzen. Deut. med. J. **6:** 574.
53. Stenzl, H., A. Staub, C. Simon & W. Baumann. 1950. Zur Kenntnis der 3-Aminopyrazolone-(5). Helv. Chim. Acta. **33:** 1183.
54. Theobald, W. Intern. Rept. I. R. Geigy Ltd. Basel, Switzerland.
55. Theobald, W. & R. Domenjoz. 1956. Der Einfluss der Adrenalektomie auf die Wirksamkeit antiphlogistischer Substanzen. Arch. Intern. pharmacodynamie. **104:** 453.
56. Theobald, W. & R. Domenjoz. 1958. Das Xerotoninoedem der Ratte und seine Beeinflussung durch Antiphlogistica. Arzneimittel-Forsch. **8:** 18.
57. Vaughan, P. 1958. The comparative effects of phenylbutazone and G 27202 (metabolite I) in patients with rheumatoid arthritis: an assessment of methods for antirheumatic drug evaluation. Arthritis and Rheumatism. **1:** 212.
58. Vaughan, P. & D. S. Howell. 1958. The comparative effects of phenylbutazone and G 27202 (metabolite I) in patients with rheumatoid arthritis. Arthritis and Rheumatism. **1:** 283.
59. Wilhelmi, G. 1949. Über die pharmakologischen Eigenschaften von Irgapyrin, einem neuen Präparat aus der Pyrazolreihe. Schweiz. med. Wochschr. **79:** 577.
60. Wilhelmi, G. 1950. Über die antiphlogistische Wirkung von Pyrazolen, speziell Irgapyrin, bei peroraler und parenteraler Verabreichung. Schweiz. med. Wochschr. **80:** 936.
61. Wilhelmi, G. 1952. Über die Retardwirkung von Dioxophenylbutyl-Pyrazolidin (Butazolidin) auf verschiedene Pharmaka, insbesondere Analgetica. Helv. Physiol. et Pharmacol. Acta. **10:** C 33.
62. Wilhelmi, G. 1954. Zur Frage peripherer Mechanismen bei der antiphlogistischen Wirkung der Pyrazole. Helv. Physiol. et Pharmacol. Acta. **12:** C 43.
63. Wilhelmi, G. 1957. Über die ulcerogene Wirkung von 5-Hydroxytryptamin am Rattenmagen und deren Beeinflussung durch verschiedene Pharmaka. Helv. Physiol. et Pharmacol. Acta. **15:** C 38.
64. Wilhelmi, G. 1958. Esperienze comparative sulle proprieta farmacologiche dei vari sali del fenilbutazone e sulla somministrazione contemporanea di acido 1-ascorbico. Farmaco (Pavia) Ed. sci. **13:** 922.
65. Wilhelmi, G. Über die pharmakologischen Eigenschaften der Metaboliten von Butazolidin ®. To be published.
66. Wilhelmi, G. Intern. Rept. I. R. Geigy Ltd. Basel, Switzerland.
67. Wilhelmi, G. & J. P. Currie. 1954. Über die pharmakologischen und klinischen Eigenschaften von G 25671 (Geigy, Basel), einem neuen Präparat aus der Pyrazolidinreihe. Schweiz. med. Wochschr. **84:** 1315.
68. Wilhelmi, G. & R. Domenjoz. 1951. Die Beeinflussung des Hühnereiweiss-Oedems an der Rattenpfote durch Pyrazole, sowie Cortison und ACTH. Arzneimittel-Forsch. **1:** 151.
69. Wilhelmi, G. & R. Domenjoz. 1951. Vergleichende Untersuchungen über die Wirkung von Pyrazolen und Antihistaminen bei verschiedenen Arten der experimentellen Entzündung. Arch. intern. pharmacodynamie. **85:** 129.

70. Wilhelmi, G., B. Herrmann & G. Tedeschi. 1959. Konzentration einiger Antipyretica im Entzündungsexsudat, sowie im Blut und ihre antiphlogistische Wirkung. Arzneimittel-Forsch. **9:** 241.

71. Wilhelmi, G. & R. Pulver. 1955. Untersuchungen zur Frage eines peripheren Angriffspunktes der Pyrazole bei der antiphlogistischen Wirkung. Arzneimittel-Forsch. **5:** 221.

72. Woolfe, A. D. & G. McDonald. 1944. Evaluation of analgesic action of pethidine hydrochloride (Demarol). J. Pharmacol. Exptl. Therap. **80:** 300.

3. Yü, T. F., J. J. Burns, B. C. Paton, A. B. Gutman & B. B. Brodie. 1958. Phenylbutazone metabolites; antirheumatic, sodium-retaining and uricosuric effects in man. J. Pharmacol. Exptl. Therap. **123:** 63.

4. Yü, T. F., T. Chenkin, B. C. Paton & V. Randolph. 1955. Effect of G 25671, a phenylbutazone analogue, on urate clearance, glomerular filtration rate and renal plasma flow. J. Pharmacol. Exptl. Therap. **113:** 57.

5. Kreppel, E. 1959. Der Einflusseiniger Phenylbutazonderivate auf den Phenolrotblutspiegel der Ratte. Medicina Experimentalis. **1.** In press.

6. Pfister, R. & F. Häfliger. 1957. Über Derivate des Phenylbutazons. I. Helv. Chim. Acta. **40:** 395.

7. Denss, R., F. Häfliger & S. Goodwin. 1957. Über Derivate des Phenylbutazons. II. Helv. Chim. Acta. **40:** 402.

8. Girod, E., R. Delley & F. Häfliger. 1957. Über Derivate des Phenylbutazons. III. Helv. Chim. Acta. **40:** 408.

9. Pfister, R. & F. Häfliger. 1960. Helv. Chim. Acta. **43:** In press.

A METHOD OF DRUG EVALUATION IN RHEUMATOID ARTHRITIS: RESULTS WITH PHENYLBUTAZONE, OXYPHENYLBUTAZONE, CORTISONE, AND PREDNISONE*

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The clinical evaluation of any new drug introduced for the treatment of patients with rheumatoid arthritis is a most difficult task, as becomes particularly evident in long-term studies made to appraise the end results of a therapeutic agent. Many experienced observers who have given thoughtful consideration to this problem have pointed out the need for more reliable methods of measuring the response of new agents in this disease.[3,9,10] This need becomes increasingly apparent as new and more potent anti-inflammatory drugs are made available for clinical investigation at an increasingly rapid rate. Ultimately their value must necessarily be tested in patients, taking into account any possible risk due to prolonged administration.

One of the major factors limiting determination of the effect of a given drug-therapy program is the lack of knowledge regarding the natural course of this notoriously variable disease. Much more information regarding the cause and prognosis of rheumatoid arthritis in patients observed for long periods is required before accurate assessments can be made. Progress is being made in this direction. The results in 174 patients treated by simple medical and orthopedic measures with an average follow-up of 14 years at the Massachusetts General Hospital have been reported recently by Short *et al.*[1] In this series, 35 per cent were classified as improved and 13 per cent were in remission after 14 years. Duthie and his associates[2,3] in Scotland have conducted similar long-term follow-up studies of 307 patients 6 years after a period of hospitalization and a subsequent conservative regimen of treatment. Evaluation showed that 24 per cent of the patients were able to carry on all normal activities, 40 per cent were moderately incapacitated, 26 per cent were more severely crippled, and only 10 per cent had become helpless and dependent on others. The disease remained active throughout the period of study in about 65 per cent of patients, whereas nearly 30 per cent showed no signs of activity. In another group of 374 patients with rheumatoid arthritis followed by Ragan[4] at the Presbyterian Hospital in New York, N.Y., 48 per cent had no arthritis or only occasional joint pain, 42 per cent had poor end results with or without active disease, and 10 per cent were either bed- or chair-ridden. In view of these and other reports, the possibility that favorable changes are due to natural remissions and unfavorable changes to relapses must be considered in any clinical trials of new drugs.

The clinical investigation reported here was designed to determine the value of various drugs used in the treatment of rheumatoid arthritis. It was undertaken with full realization of the pitfalls in the existing methods for judging

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benefit, but with the hope of devising and applying some new control methods and perhaps offering data that would be statistically valid.

Anyone who has made a serious attempt to grade the results of therapy in rheumatoid arthritis recognizes that there are symptomatic responses that are so elusive and personal that they cannot be evaluated on a statistical basis. Unfortunately, these are the very factors about which the patients are most concerned—stiffness, muscle spasm, weakness, anorexia, fatigue, and lack of sense of well-being. The method that forms the basis of this report does not include an appraisal of these subjective responses, which cannot be accurately determined. The data recorded were based on objective findings obtained upon examination of the patient, and incorporating the principles of the double-blind technique. The results are expressed in numerical indices of changes in the functional capacity and joint inflammation. Preliminary reports on this method were given in 1957[5] and 1959.[6] Modifications made in subsequent, more extensive, trials have simplified measurement, so that now this quantitative method is practical for clinical trials. It is reliable and sufficiently sensitive to changes produced by drug administration, and the measurements are reproducible.

To illustrate the application of this method, the data obtained during the first 3 years of this study of 58 patients will be reviewed. These patients received as test drugs phenylbutazone, cortisone, or prednisone for periods of 5 months; the results have been compared with those following treatment with aspirin. In the last year 20 additional patients have received oxyphenylbutazone for periods of 1 and 2 months, and the results with this anti-inflammatory drug have been compared with those following 1 month of aspirin therapy.

Method of Study

Selection of patients. Two experienced clinicians concurred in the diagnosis, which was based upon the usually accepted clinical and laboratory criteria. The disease had been present for at least one year, and patients with cardiac failure, history of peptic ulcer, renal disease, or anemia were excluded from the study.

Administration technique. All drugs were identical, but code-labeled, tablets. In the first three years the test drugs were phenylbutazone, cortisone, and prednisone.* The order in which each test drug was administered was randomized and unknown to both patient and physician (double blind). During the last year when aspirin and oxyphenylbutazone were administered, the physician but not the patient was aware of the drug being administered; in this phase of the study the single-blind technique was employed.

Drug sequences. During the first 3 years of this study the 3 test drugs were administered in a variable sequence, each period on 1 test drug being preceded and followed by an interval on aspirin (TABLE 1). The duration of each test drug period was 5 months and the period of aspirin administration was 1 month.

During the last year of this study, when oxyphenylbutazone was the drug investigated, the duration of each test period was 1 month. In each instance there was an interval of 1 month on aspirin preceding and following oxyphenylbutazone. However, as the period on the test drug may have been inadequate, these data are considered to be preliminary.

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* The prednisone was supplied as Meticorten by the Schering Corporation, Bloomfield, N.J.

Dosage. The number of tablets prescribed per day was variable, being governed by the subjective response of the patient. The total daily dose of phenylbutazone ranged from 50 to 800 mg./day; cortisone, 25 to 150 mg./day; prednisone, 2.5 to 40 mg./day; oxyphenylbutazone, 100 to 400 mg./day; and aspirin, 900 to 2,400 mg./day. In some cases the number of pills was restricted because of the appearance of signs of toxicity.

Plan of follow-up. On initiation of therapy and after each period on the test drug or aspirin, objective measurements of joint inflammation and function were made by the method described below. The erythrocyte sedimentation rate (ESR), white blood cell count, and hematocrit were determined and the sensitized sheep red blood cell agglutination test as modified by Ziff[7] was made before drug therapy was begun and after change in medication. Serial roentgenograms were obtained at 6-month intervals. The changes in osteoporosis, joint space narrowing, erosion, and deformity were scored by 3 experienced observers. Since the 5-month test period on each drug was found to be too short to reflect any consistent changes, X-ray studies were discontinued after the second year.

TABLE 1

Drug sequence	Aspirin	1st Test drug	Aspirin	2nd Test drug	Aspirin	3rd Test drug	Aspirin
Time on drug (months)	1	5	1	5	1	5	1
Evaluation examination	1	2	3	4	5	6	

Measurements

Inflammatory index. In the early phases of this study attempts were made to relate the degree of inflammation to the percentage of total articulating surface by means of the joint surface measurements of Lansbury and Haut.[8] This gave undue emphasis to large joints, such as the hips and shoulders, where accurate measurements by clinical methods were impossible. In the method discussed here, the degree of joint inflammation is expressed in terms of the classic clinical signs of inflammation: pain, heat, redness, and swelling, plus the presence of joint fluid. Paired joints were judged together and the amount of each element of inflammation was recorded on a scale of positive values ranging from + to ++++. In each examination, the total positive score for all joints was used as a numerical index of the total amount of inflammation. This inflammatory index was recorded at the end of each test-drug and aspirin-treatment period (FIGURE 1).

Functional index. The ability of the patient to perform daily tasks cannot constitute a quantitative measure of over-all functional capacity. Instead, measurements of three functions have been found to give reliable data. These three objective tests are simple to perform and have been shown to be sufficiently sensitive to reflect changes due to the influence of drug action. The results of these three tests of functional capacity were combined by a simple ranking system to express an index of comparative response to each drug. The tests are as follows:

(1) Distance between styloid process and acromioclavicular joint. The upper arm is held flexed at a 45° angle and the elbow flexed with the thumb pointing toward the acromioclavicular joint. The distance between the styloid process at the wrist and the anterior margin of the acromioclavicular joint can be measured accurately (FIGURE 2).

(2) Grip test. The power of the grip was measured by use of an ordinary sphygmomanometer cuff loosely rolled and the bag inflated to between 20 and 30 mm. Hg. The patient squeezed the bag as hard as he could. The sum of the readings of the Hg column for both hands is the value recorded.

Joint inflammation	Pips	M Ps	Wrists	Elbows	Shoulders	Hips	Knees	Ankles	Feet	Score
Initial exam										
Swelling	+	+	+	+						26
Redness										
Heat			+	+						
Tenderness	+	+	++	+++			++		++	
Pain	+	+	++	++	+		+		+	
Fluid										
Exam after 5 months										
Swelling				+						5
Redness										
Heat										
Tenderness				+			+			
Pain				+						
Fluid							+			
Exam after 6 months										
Swelling		+	+	++			+			30
Redness		+								
Heat		+	+	+						
Tenderness		+	++	++	++		++	++	++	
Pain			++	++	+++					
Fluid				+						

FIGURE 1. Data form used for recording joint inflammation, showing the findings in one patient at the initial and two subsequent examinations. The sum of plus values for all joints was 26 at the first examination, 5 at the second, and 30 at the third.

(3) Walking time. The time a patient takes to walk 25 feet is a measure of function of the joints of the lower extremities. The patients were allowed to use crutches if necessary.

Statistical Methods

The statistical design of this study required that each patient be evaluated with regard to function and inflammation for each test-drug sequence, with aspirin serving as the control drug. Thus the response to the test drug (aspirin–test-drug sequence) as well as the subsequent response (test-drug–aspirin sequence) could be observed. Throughout the study only paired measurements were used in the analysis. Many other single measurements were obtained, but these were omitted in favor of fewer paired observations, which

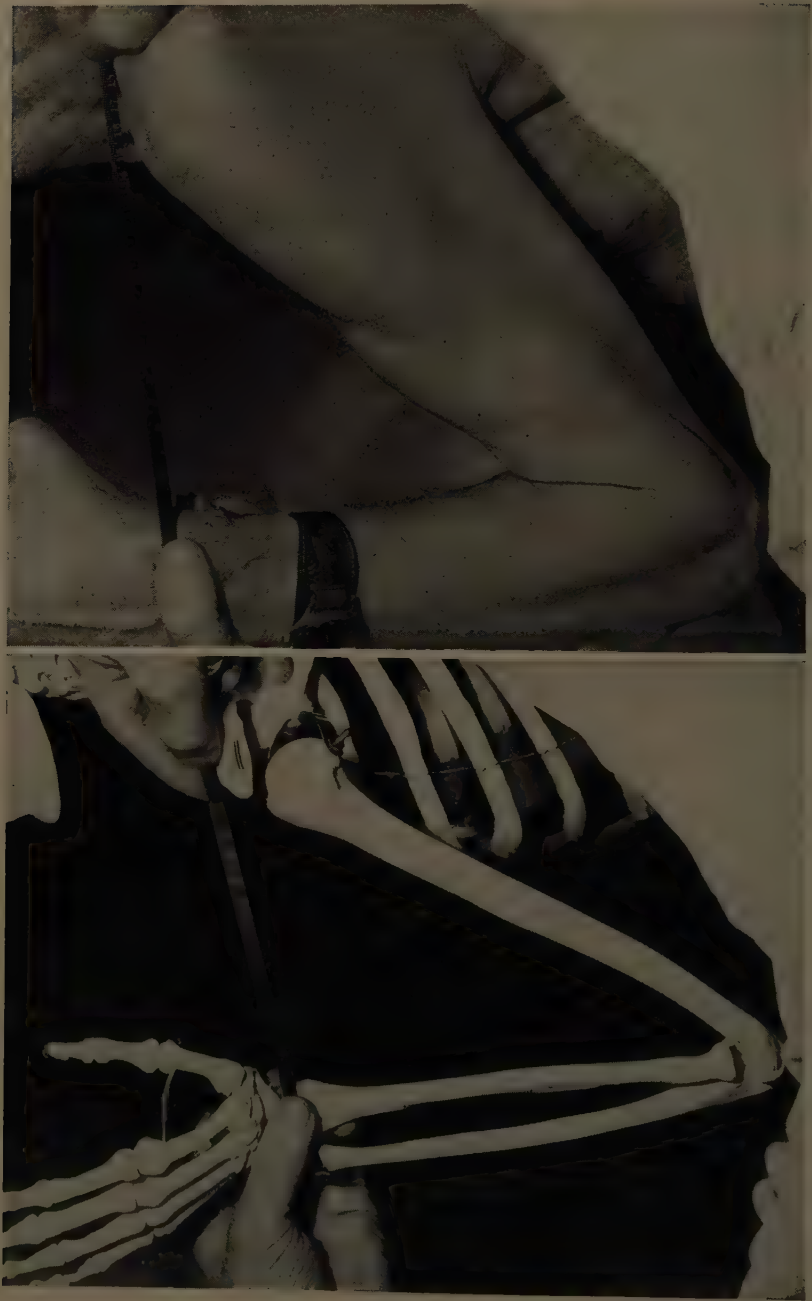

FIGURE 2. The bony landmarks used in the styloid-acromioclavicular distance are easily located.

permitted a far more sensitive analysis. Thus related sample data were available, allowing a rigid evaluation of the effectiveness of each test drug.

Both parametric and nonparametric statistics were used. On occasion, nonparametric methods resulted in more significant responses; in general, however, similar results were obtained with both methods of analysis.

The three tests of functional capacity resulted in values of different dimensions and changes of different signs as a consequence of drug therapy. In addition, the patients who had been evaluated on one drug sequence were not necessarily the same as those on another sequence. To express the results as simply and yet as reliably as possible, a ranking system combining results of the three tests was chosen. For a given drug sequence, the responses were ranked in magnitude and direction for each test. The algebraic sum of these values was obtained and divided by the sum of the absolute values, that is, the sum that would denote a perfect score.

The inflammatory index was simple to compute. Since all measurements were comparable, the index was merely the sum of all plus values obtained by the standard method of recording joint inflammation as presented above.

Recording of Toxic Reactions

Undesirable reactions including fluid retention, moon-face, gastrointestinal symptoms, purpura, drop in blood count to below 5,000 per cu. mm., infections, rash, and other undesirable effects were elicited by verbal and physical examination on each visit and by periodic checks of weight, blood count, and urinalysis. The patients were warned to report immediately any unusual symptoms.

Application of Method

Results with phenylbutazone, cortisone, and prednisone. A total of 58 patients was given at least 1 drug sequence (aspirin–test drug–aspirin), and 16 patients had the complete series of 3 test drugs, or 6 drug sequences, which permitted assessment of bidirectional changes.

Changes in functional capacity. The results obtained with two patients given walking-time and grip tests are illustrated in FIGURES 3 and 4, respectively. Data for one function test, the time taken by the patient K.Y. to walk 25 feet, were recorded for all 6 drug sequences. The stippled perpendicular bars marked A represent measurements following 1-month periods on aspirin. At the end of the first period of therapy the time taken to walk this fixed distance was 20 sec. After 5 months of cortisone therapy this decreased to 9 sec. When the sequence was reversed and the patient was placed again on aspirin after receiving cortisone, the time required increased from 8 to 15 sec. In the middle of FIGURE 3 are recorded the data for K.Y. when shifted from aspirin to phenylbutazone and from this test drug back again to aspirin. The patient's walking time changed from 30 to 12 sec. and from 12 to 10 sec. On the right side of the chart are recorded the results of the drug sequence aspirin–prednisone–aspirin, during which the time decreased from 15 to 9 sec. and then increased from 8 to 23 sec.

Gripping strength, as measured by a patient's ability to squeeze the folded cuff of a mercury manometer, changed more radically; data for the patient

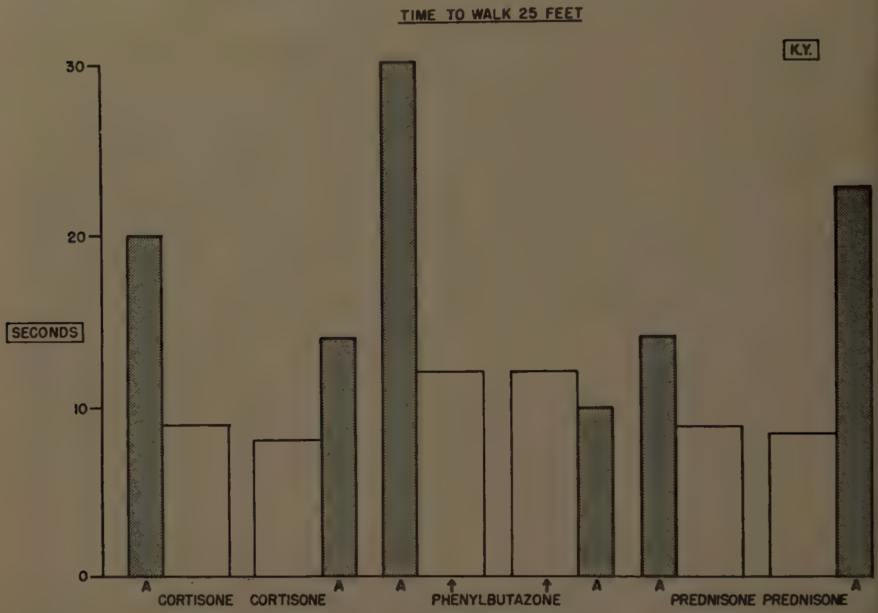

FIGURE 3. Data for one patient, showing the time taken in the walking test (sec.), 3 drugs. Each period of 5 months on the test drug was preceded and followed by a period of 1 month on aspirin (A).

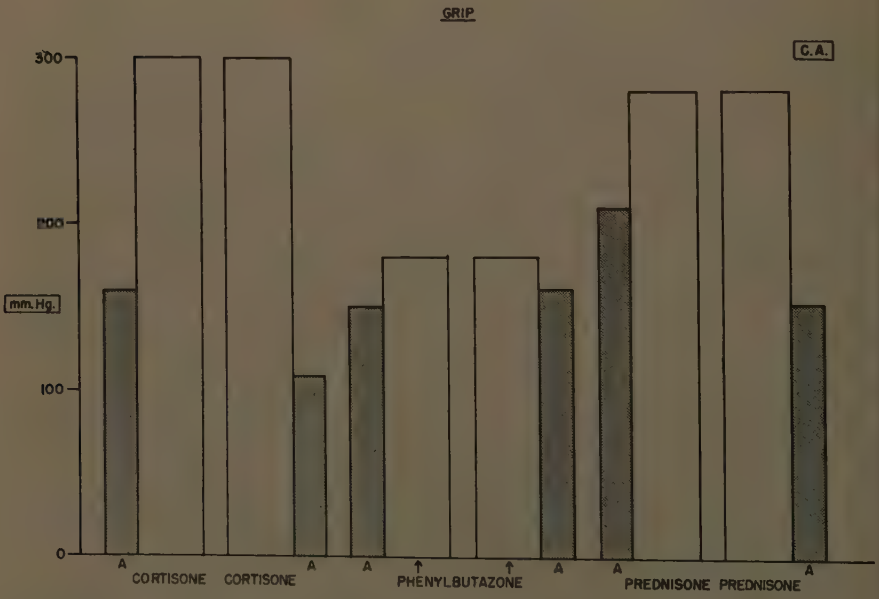

FIGURE 4. Data for one patient showing changes in gripping power in mm. Hg, all 6 drug sequences.

C.A. are illustrated in FIGURE 4. The stippled bars (A) represent measurements following 1-month periods on aspirin; the other bars represent measurements following cortisone, phenylbutazone, and prednisone treatments. In each instance the better the function, the higher the Hg column rose. When the drug shift was aspirin to cortisone, the power of the grip increased from 160 to 300 mm. Hg, and when the shift was reversed it dropped from 300 to 110 mm. Hg. A similar change occurred for the aspirin–prednisone–aspirin shift; a smaller change was recorded for the drug sequence aspirin–phenylbutazone–aspirin.

To express the total change in functional capacity of a patient for each drug sequence, the results of the functional capacity tests recorded in seconds (walking test), centimeters (range of elbow motion), and mm. Hg (gripping strength) were combined by a simple ranking system and expressed as an index. This was necessary since the dimensions and magnitude of changes in each test were completely different and it was desirable to express all changes on a common scale. Thus it was possible also to compare patients' responses.

As an illustration, the functional index for gripping strength and the drug sequence aspirin–cortisone is developed in TABLE 2 from data on 30 patients. The difference scores are obtained from the second and third columns. These differences are then ranked, in this case from 1 through 30, the rankings corresponding in sign to the differences. A functional index of ±100 for a group would be obtained if all the ranks were of the same sign, that is, if all responses were in the same direction. For the data on gripping strength, the total score (sum of the absolute values of all ranks) is 465. The sum of the negative ranks (total improvement) is −367. Thus, by the simple computation shown in TABLE 2, the functional index is −81, the negative index denoting, in this case, a positive response to the drug tested. Indices for the other two measurements of function, walking time and stylo-acromioclavicular distance, were obtained by similar methods.

When the data from all three functional tests were combined properly, a final functional index for each drug sequence was obtained (FIGURE 5). Thirty-one patients were given the drug sequence aspirin–cortisone; 30, cortisone–aspirin; 30, aspirin–phenylbutazone; 30, phenylbutazone–aspirin; and 25 and 26, aspirin–prednisone and prednisone–aspirin, respectively.

The mean functional index associated with the change from aspirin to cortisone was +58 (where + signifies increased function); the index for the cortisone–aspirin sequence was −60. The aspirin–phenylbutazone index was +28, and it was surprising that the reverse sequence of these drugs resulted in an index of only −7. The aspirin–prednisone index was +50, whereas the index for the reverse sequence was −58.

Anti-inflammatory response. The degree of joint inflammation, the presence of clinical swelling, redness, heat, tenderness, pain on motion, and fluid were recorded by standard methods, converted to numerical values, and expressed at the end of each test period as an index of total inflammation.

Typical examples of changes in the inflammatory index measurements for two patients, F.C. and N.C., are shown in FIGURE 6. Each of these patients had all six drug sequences. The change in inflammation in the case of F.C. was distinctly less than that in N.C. (note that the range of the ordinate in

F.C.'s chart is less than that in N.C.'s). There is a striking similarity between the response of inflammation to drug therapy, as shown here, and the previous illustrations of changes in functional capacity.

The percentage changes accompanying the aspirin–cortisone–aspirin and the aspirin–prednisone–aspirin shifts are marked in the case of F.C. A less marked but definite reduction occurred in the inflammatory index for the aspirin–phenylbutazone–aspirin sequence. N.C. responded similarly.

TABLE 2
FUNCTIONAL INDEX OF GRIPPING STRENGTH

Patient	Aspirin, mm. Hg	Cortisone, mm. Hg	Difference	Rank
W.Mc.	384	600	−216	−30
W.J.	324	519	−195	−29
L.Co.	190	378	−180	−28
C.A.	159	319	−151	−27
M.L.	140	265	−125	−26
I.D.	117	222	−105	−25
R.G.	126	230	−104	−24
D.E.	187	266	−79	−22.5
C.Mi.	404	483	−79	−22.5
K.Y.	212	281	−69	−21
M.Veg.	450	511	−61	−20
F.C.	390	335	+55	+19
E.B.	213	168	+45	+18
C.Ma.	77	120	−43	−17
L.Ha.	250	283	−33	−16
Mg.J.	167	135	+32	+15
N.C.	140	170	−30	−14
J.R.	278	306	−28	−13
M.F.	135	159	−24	−11
H.O.	284	260	+24	+11
F.S.	112	136	−24	−11
J.M.	439	418	+21	+9
V.P.	125	105	+20	+7.5
E.S.	100	120	−20	−7.5
Mr.J.	151	167	−16	−6
S.J.	170	156	+14	+5
O.B.	120	132	−12	−4
M.G.	158	150	+8	+3
L.C.	55	50	+5	+1.5
C.C.	135	140	−5	−1.5

Total score (sum of absolute values of all ranks) 465
Response (sum of negative ranks only: total improvement) −376

$$\text{Functional index} = \frac{\text{response}}{\text{total score}} \times 100 = \frac{-376}{465} \times 100 = -81$$

The data relative to changes in the inflammatory index in the 58 patients studied and for all drug sequences are combined in FIGURE 7. The number of patients given each of the six drug sequences is shown across the top of the chart. Increased inflammation is shown above the middle horizontal line and given a plus sign and decreased inflammation is recorded below the line and indicated by a minus sign. The aspirin–cortisone sequence resulted in a significant decrease in inflammation; inflammation increased, however, when 29 of the patients were given the reverse sequence. Similar but greater changes followed the aspirin–prednisone to prednisone–aspirin sequences and these values were also significant. A definite and significant decrease resulted from the aspirin-phenylbutazone sequence given to 31 patients, but it is noteworthy that the 28 patients on the phenylbutazone-aspirin sequence did not experi-

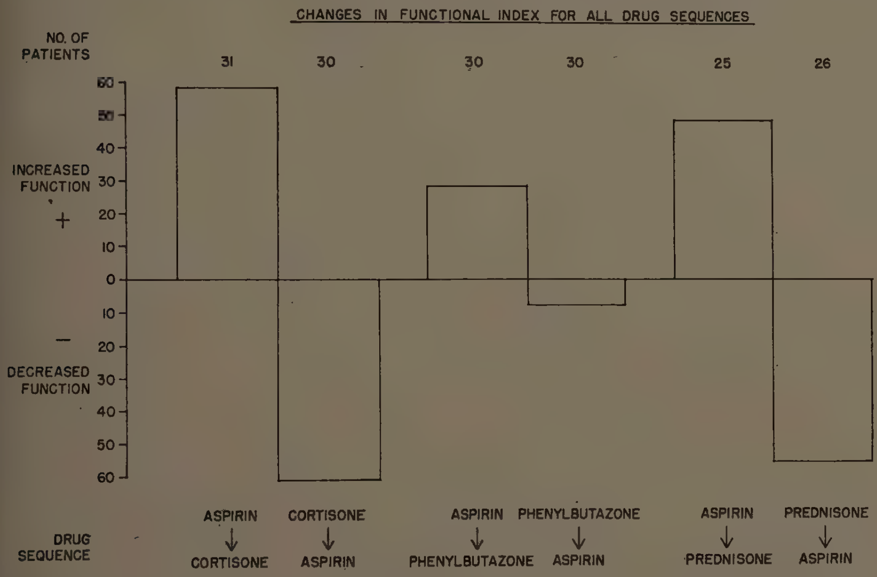

Figure 5. Summary of all measurements of the functional index. The bars represent mean changes in function due to each drug. The drug sequence appears at the bottom of the diagram.

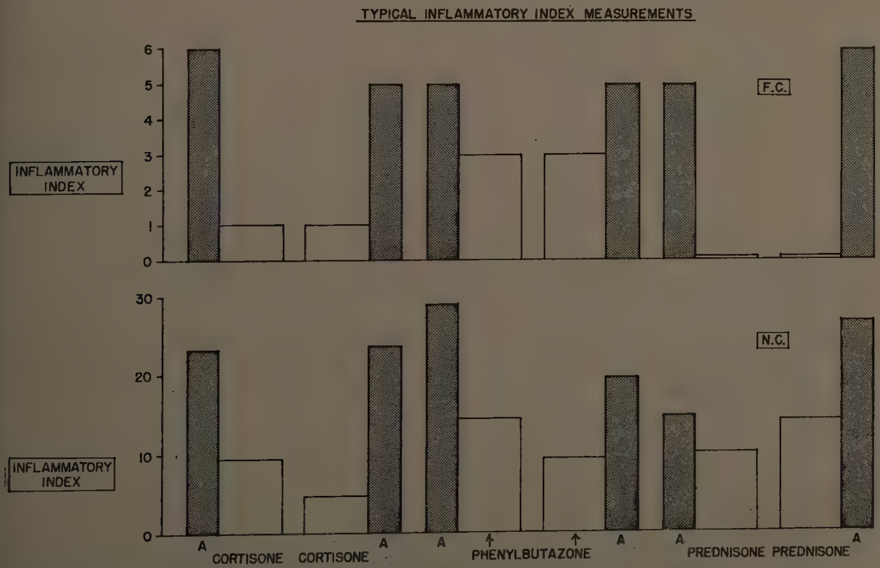

Figure 6. Inflammatory index changes in 2 patients following all 6 drug sequences.

ence a significant return of the inflammation after the one month on aspirin therapy. It would appear that this drug has a more prolonged anti-inflammatory effect than either of the two steroid preparations used in this study.

Results with oxyphenylbutazone. The measurements on 20 patients receiving oxyphenylbutazone were made following treatment periods shorter than those used with the other 3 drugs. It is emphasized that in this phase of the study the single-blind technique was used: the physician responsible for the recordings was aware of the drug being administered, but the patient was not.

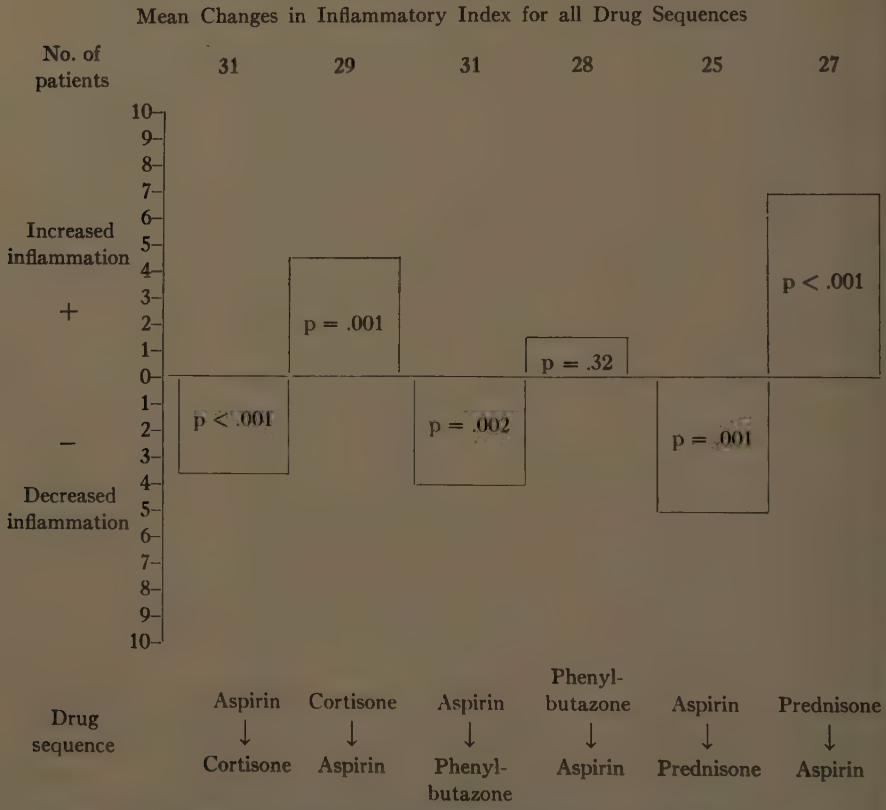

FIGURE 7. Summary of changes in inflammation in all patients with all drug sequences. All changes are significant except that due to the phenylbutazone–aspirin sequence (p = 0.32).

FIGURE 8 is a summary of the data obtained following administration of this drug as compared with the data following aspirin. The inflammatory index is shown on the left-hand side of the chart and the functional index on the right. The numbers of patients treated with each drug sequence are shown across the top of the chart. For the inflammatory index observations, 16 patients were placed on aspirin first and 8 were given phenylbutazone first. Changes in functional capacity were recorded in 14 patients receiving aspirin–phenylbutazone, and in 7 treated with the reverse sequence.

As in the previous summary charts, the direction of change is shown by plus values above and minus values below the horizontal line. It will be noted that the degree of clinical inflammation decreased and functional capacity improved when the patients were placed on oxyphenylbutazone. The situation was reversed when the patients were shifted from oxyphenylbutazone to aspirin. The amount of data in this phase of the study is too small to be statistically significant, but the trend is evident.

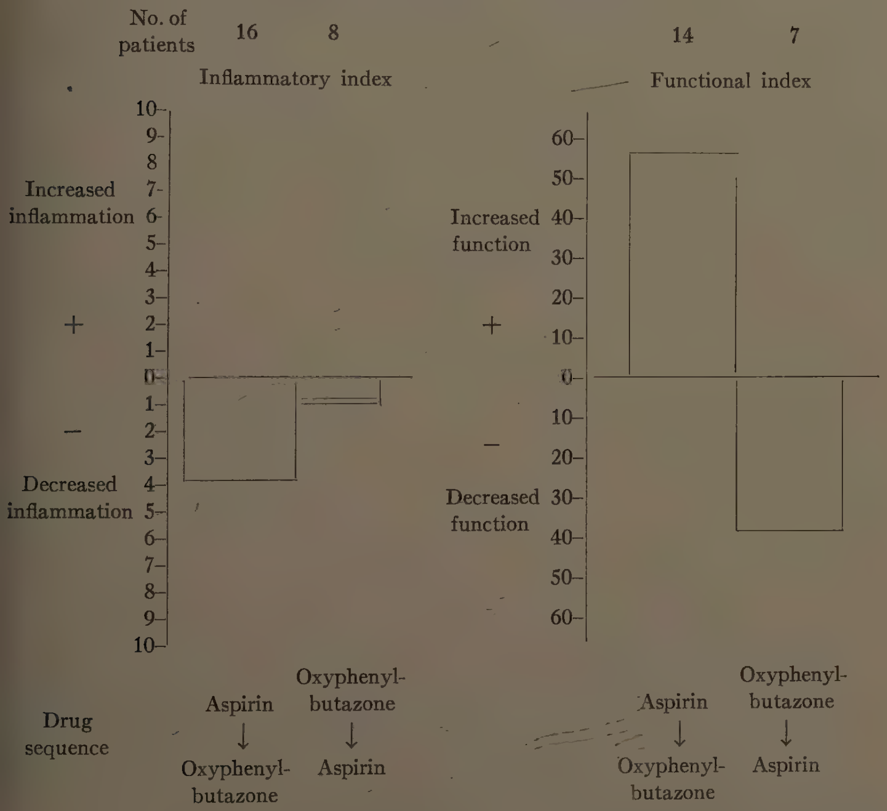
Effects of Oxyphenylbutazone on Rheumatoid Arthritis

FIGURE 8. The small size of the group receiving the drug precludes statistical analysis, but the trend appears to follow that obtained with phenylbutazone with respect to both inflammatory and functional indices.

Hematopoietic changes with oxyphenylbutazone. Among the 20 patients with rheumatoid arthritis there were three whose blood changed significantly while they were receiving this drug.

Patient K.P., a female aged 55 years, had been receiving 200 mg. of oxyphenylbutazone daily for 6 weeks when it was observed that the white blood cell count was 4000 per cu. mm. The drug was continued for 3 more days and a second white blood cell count revealed 2900 per cu. mm. Examination showed no abnormal white blood cells in the blood smear. The drug was discontinued, and the white blood cell count was determined again 2 weeks later.

The count had returned to 6000 per cu. mm., the pretreatment level. It is of interest that this patient had experienced an undefined blood reaction to phenylbutazone in 1954, so that this drug had to be discontinued.

The second patient in whom a hematopoietic change was observed was a 73-year-old white female who had received oxyphenylbutazone for 4½ months in doses of 150 mg./day. She was hospitalized for cholecystectomy, and during this time the drug was discontinued. When it was resumed in 200-mg. daily doses, the white blood cell count was found to be 4000 per cu. mm., and the differential count revealed that the number of polymorphonuclear neutrophils had decreased to 28 segmented and 4 unsegmented cells. The drug was stopped and the white blood cell count returned to normal during the next four weeks.

The third patient was a 45-year-old female who had received 300 mg. of oxyphenylbutazone daily for 4 weeks. She became progressively weaker and was nauseated. An upper gastrointestinal X ray was normal. The hemoglobin dropped from a pretreatment level of 10.0 gm. per cent to 5.9 gm. per cent, with no change in the white blood cell count. The patient was hospitalized and the drug was discontinued. The stools were found to be positive for blood, and proctoscopic examination revealed a benign polyp. The blood loss obviously accounted for the anemia, and a series of transfusions brought the blood count back to normal. The drug was started again and no further changes in the blood have been observed. This hematopoietic complication was not related to the administration of oxyphenylbutazone.

TABLE 3
SIGNIFICANCE OF ESR MEASUREMENTS

Drug sequence	Number of patients	Mean ESR		Significance (p)	Responses in expected direction (%)
		Aspirin	Test drug		
Aspirin-cortisone	19	37	33	0.11	63
Cortisone-aspirin	20	35	33	0.20	50
Aspirin-phenylbutazone	24	34	34	1.00	50
Phenylbutazone-aspirin	22	30	32	0.38	41
Aspirin-prednisone	22	33	26	0.04	68
Prednisone-aspirin	21	37	30	0.05	67

Laboratory results. The erythrocyte sedimentation rate taken at the time of each clinical measurement was not a reliable index of inflammatory change. Although the erythrocyte sedimentation rate changes tend to follow the results of drug administration, they are very insensitive in reflecting activity. Since ESR tests are used in some of the currently recommended methods of drug evaluation in patients with rheumatoid arthritis, the data from the current study are submitted in detail (TABLE 3). It is notable that most of the ESR results are not significant.

For the aspirin–cortisone drug sequence, the mean sedimentation rate dropped from 37 to 33 mm. per hour, with the expected decrease occurring in 63 per cent of the cases. The size of the decrease, however, is not significant (p = 0.11). Similarly, as a result of the cortisone–aspirin drug sequence, the ESR rose from 33 to 35 mm. per hour, with increases occurring in 50 per cent of the patients. This rise is not significant.

There was no significant change in the erythrocyte sedimentation rate due to the aspirin–phenylbutazone drug sequence. Changes in the sedimentation rate due to aspirin–prednisone and prednisone–aspirin were barely significant. The data obtained during the administration of oxyphenylbutazone are inadequate for evaluation. It will be noted that for all drugs on which adequate data were obtained, the sedimentation rate changed in the expected direction only 57 per cent of the time, on the average. Since most of the data are not significant, this test is not considered reliable as an index of drug effectiveness.

Comparison of data taken in the sensitized sheep red blood cell agglutination test with mean inflammatory index measurements did not reflect any responses to drug therapy.

Serial roentgenograms of the small joints of the hands, wrists, and feet proved to be the most valuable for the detection of progressive involvement of cartilage and bone. Five months on a test drug was too short a period, however, for any consistent changes to be reflected in the roentgenograms. The films were read separately by three experienced observers.

Summary

An objective method for the measurement of the clinical response of drug therapy in rheumatoid arthritis is presented. It is based upon a series of simple measurements of functions and joint inflammation. Bidirectional evaluation of the test drugs was used, since it is a stronger test than evaluation by a single sequence. These tests are easy to perform, reproducible, and sufficiently sensitive to reflect changes produced by some of the currently available anti-inflammatory drugs.

In this 4-year study, 58 patients were treated with phenylbutazone, cortisone, and prednisone, and 20 patients were treated with oxyphenylbutazone. In all instances the results were compared with those following the administration of aspirin. Marked changes in the inflammatory index followed the use of prednisone. Changes in the inflammatory index produced by phenylbutazone and cortisone were about equal. Improvement in functional capacity as reflected in changes in the functional index as a result of cortisone and prednisone were comparable; less marked improvement followed the administration of phenylbutazone.

It is of interest that the aspirin–phenylbutazone–aspirin sequence resulted in minimal abnormalities in both function and inflammation. This suggests that phenylbutazone has a more prolonged effect than either cortisone or prednisone.

Oxyphenylbutazone appeared to be as effective an anti-inflammatory agent in rheumatoid patients as phenylbutazone. More prolonged study will be required to determine its toxicity.

It is hoped that these observations will serve as a stimulus to other investigators and as a basis for development of sounder methods for evaluating therapy in this variable disease.

Acknowledgments

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References

1. Short, C. L., W. Bauer & W. E. Reynolds. 1957. Rheumatoid Arthritis. Published for the Commonwealth Fund. Harvard Univ. Press. Cambridge, Mass.
2. Duthie, J. J. R., M. Thompson, M. M. Weis & W. B. Fletcher. 1955. Medical and social aspects of the treatment of rheumatoid arthritis. Ann. Rheumatic Diseases. **14:** 133–149.
3. Duthie, J. J. R., P. E. Brown, J. D. E. Knox & M. Thompson. 1957. Course and prognosis in rheumatoid arthritis. Ann. Rheumatic Diseases. **16:** 411–424.
4. Ragan, C. 1952. Rheumatoid arthritis: the natural history of the disease and its management. *In* The Musculoskeletal System. M. Ashford, Ed. Macmillan. New York, N.Y.
5. Smyth, C. J. & G. M. Clark. 1957. Phenylbutazone in rheumatoid arthritis. J. Chronic Diseases. **5:** 734–750.
6. Smyth, C. J., R. L. Johnson & G. M. Clark. 1959. Drug evaluation in rheumatoid arthritis. Postgrad. Med. **25:** 315–324.
7. Ziff, M., P. Brown, J. Badin & C. McEwen. 1954. A hemagglutination test for rheumatoid arthritis with enhanced sensitivity using the euglobulin fraction. Bull. Rheumatic Diseases. **5:** 75–76.
8. Lansbury, J. & D. D. Haut. 1956. Quantitation of the manifestations of rheumatoid arthritis. IV. Area of joint surfaces as an index of total joint inflammation and deformity. Am. J. Med. Sci. **232:** 150.
9. Wallace, S. L. & C. Ragan. 1958. The problem of therapeutic evaluation in rheumatoid arthritis. Arthritis and Rheumatism. **1:** 20–28.
10. Lansbury, J. 1957. Numerical method of evaluating the status of rheumatoid arthritis. Ann. Rheumatic Diseases. **16:** 101–107.

THE EFFECT OF OXYPHENBUTAZONE ON PAIN RELATED TO VASCULAR DISEASE

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A versatile family of drugs, phenylbutazone and its derivatives, affords relief of pain in various disease conditions by virtue of its analgesic, anti-inflammatory, uricosuric, or antipyretic properties.[1-3] In disorders of the peripheral circulation only the first two actions seem operative.

Acute closure of a peripheral artery causes severe and unremitting pain because collaterals do not have time to develop. Of the 15 of our patients with acute embolism or thrombosis of the main artery in a limb, not one experienced effective pain relief with oxyphenbutazone. A measure of relief was obtained by the liberal use of narcotics, but more adequate relief resulted from the restoration of blood flow through embolectomy or arterial grafting.

The severity of intermittent claudication is more variable than the pain that follows acute arterial closure. Since the depletion of the vascular bed is gradual, permitting the development of collaterals, pain or discomfort occurs only when the extremity is put to the test of use, and it subsides with rest. Additional factors, such as the tempo and type of exercise and the compensatory channels that are present and available, influence the likelihood of a painful reaction. Thirty-five patients with arteriosclerotic peripheral disease and moderate limitation of walking were treated with oxyphenbutazone for 2 weeks. Although on occasion improvement in ability to walk was striking, for the most part relief of intermittent claudication was inconstant and equivocal. In summary, oxyphenbutazone plays a negative role in the management of ischemic pain due to acute or chronic arterial closure, because its analgesic action is not of a sufficiently high order.

In sharp contrast is the striking relief of pain in inflammatory disorders of the peripheral veins[4-7] brought about by both phenylbutazone and its analogue, oxyphenbutazone. The outpouring of inflammatory cells and exudate in experimental thrombosis are suppressed.[8] We have used the two drugs interchangeably in our studies.

An inflammation of the marginal vein of a rabbit's ear can be induced readily by an irritant, and the sequence of events in the ensuing reaction can be followed at intervals. By the ninth hour, a striking difference is apparent (FIGURE 1). Only a few white cells and a little fibrin can be seen in the protected, or drug-treated, animal. The thrombus is small and spongy. In the unprotected or control animal, the clot is large, and there is marked exudation of cells, fibrin, and fluid in the vein wall and in the interstitial tissues. By the twenty-fourth hour (FIGURE 2), the difference is more marked. Histologically, the ear of the protected animal is very much like a normal ear. The ear of the control animal, however, contains a massive infiltrate of fibrin, cells, and fluid, and so distended is the vein wall that rupture with hemorrhage into the interstitial tissues occurs. A somewhat similar picture can be seen in the peripheral veins of a human (FIGURE 3).

These drugs are so specific and so potent in suppressing and limiting inflammation that they have found extensive use in the treatment of thrombophlebitis of the superficial and deep veins.

Although our clinical experience with oxyphenbutazone is not as extensive

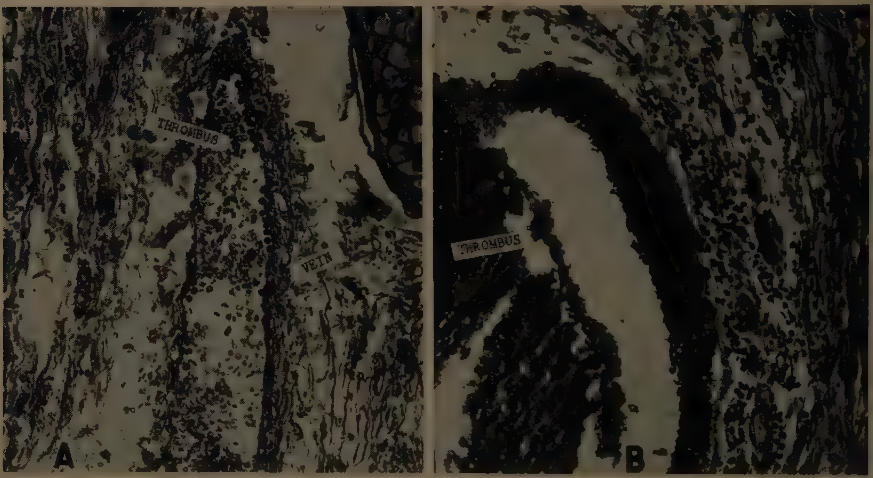

FIGURE 1. Photomicrograph (×360) 9 hours after thrombosis of marginal vein in rabbit's ear. (*A*) Small, spongy clot present inside vein, with some leukocytes at the periphery and a few in the perivascular space. This is a protected ear. (*B*) A comparison with a section of the ear in the control animal shows the large fibrin clot with marked infiltration of leukocytes into the tissues.

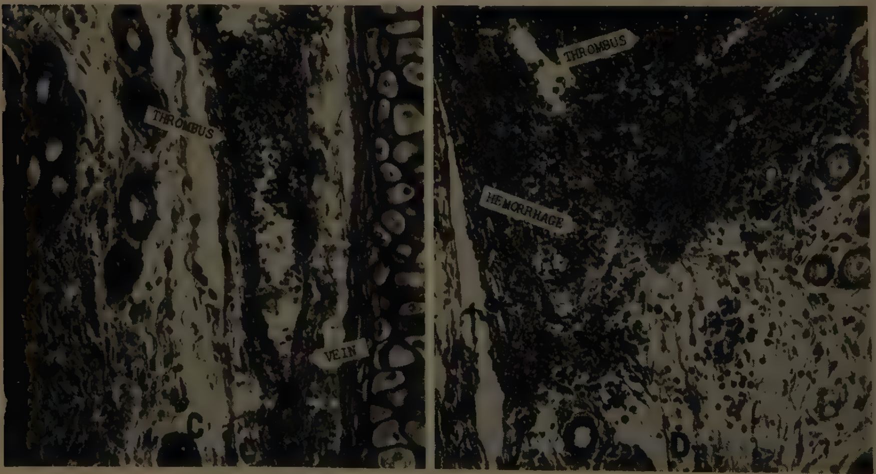

FIGURE 2. Photomicrograph 24 hours after thrombosis. (*C*) Section from a protected animal showing a small clot and practically no inflammatory reaction in the tissues. (*D*) In the control animal, a healthy clot with hemorrhage into the tissues and a heavy leukocytic infiltration.

as that with phenylbutazone, we have noted impressive clinical improvement (TABLE 1).

With proper dosage* a predictable pattern of improvement becomes apparent. Subsidence of pain and discomfort due to the inflammation in the tissues is noted by the eighth to the twelfth hour. Some use of the limb with little or no pain and even walking are possible by the twenty-fourth hour. At this time swelling, redness, and the local tenderness of the inflamed vein segments begin to wane. Fever declines, and the body temperature and pulse return to normal. In deep thrombophlebitis, edema persists as evidence of the mechanical block in the main vein, but is usually not massive or troublesome, being present chiefly in the upright position and readily controlled by elastic compression. It is theoretically possible that the venous flow is not retarded by the porous and spongy clot noted in the microscopic sections of the

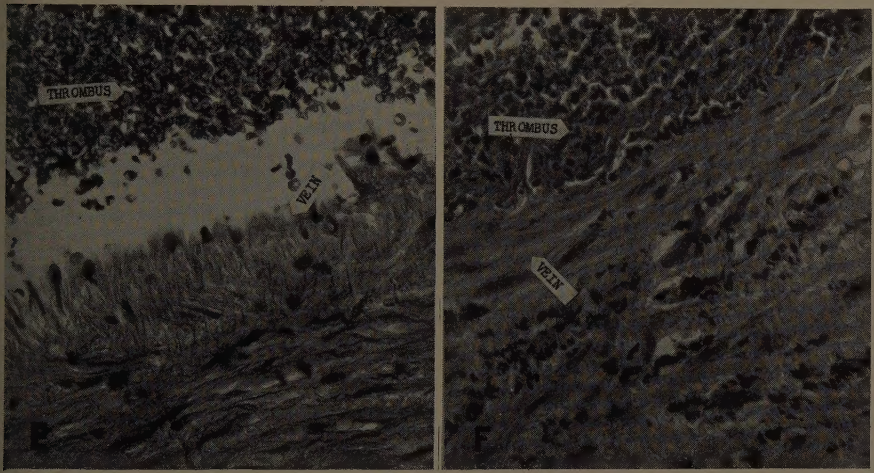

FIGURE 3. Photomicrographs of experimentally produced thrombosis in the saphenous vein of the human. (*E*) A quiescent state during treatment with phenylbutazone. The vein wall is normal in appearance, there is no fluid exudate, and only a few polymorphonuclear leukocytes are seen in the tissues. (*F*) A turbulent state. Note the edema and disruption of the normal pattern of muscle fibers, the outpouring of fluid and fibrin, and the rich infiltrate of leukocytes and lymphocytes.

TABLE 1*

THROMBOPHLEBITIS PATIENTS TREATED WITH OXYPHENBUTAZONE

Veins involved	Patients treated	Patients markedly improved	Per cent improved
Superficial (lowers)	123	112	91
Deep (lowers)	32	28	88

* From I. D. Stein and B. Rockliff, to be published.

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* Two hundred mg. 3 times a day for 3 days, then 100 mg. 3 times a day for the next 4 days (a total of 3 gm.).

drug-protected animals as completely as in untreated animals; certainly it facilitates quicker and more effective recanalization of the thrombus.

In conclusion the phenylbutazone series, by virtue of its high anti-inflammatory potential, is of practical value in the treatment of thrombophlebitis. Its rapid, reproducible and economical action, as well as its lack of side effects, have made its use a rational clinical approach to the management of this common problem.

References

1. Wilhelmi, G. 1949. Über die pharmakologischen Eigenschaften von Irgapyrin, einem neuen Präparat aus der Pyrazolreihe. Schweiz. med. Wochschr. **79:** 577.
2. Wilhelmi, G. & R. Domenjoz. 1950. Vergleichende Untersuchungen über die Wirkung von Pyrazolen und Antihistaminen bei verschiedenen Arten der experimentellen Entzündung. Arch. exptl. Pathol. Pharmakol. **212:** 125.
3. Domenjoz, R. 1955. Pharmakotherapeutische Weiterentwicklung der Antipyretika-Analgetika. Arch. exptl. Pathol. Pharmakol. **226:** 125.
4. Sigg, B. 1952. Die Behandlung der akuten Thrombophlebitis mit Irgapyrin. Praxis. **41:** 1072.
5. Sigg, K. 1954. Über die Behandlung der Phlebitis mit Butazolidin. Praxis. **43:** 172.
6. Stein, I. D. & O. A. Rose. 1954. Treatment of superficial thrombophlebitis with phenylbutazone. Arch. Intern. Med. **93:** 899.
7. Stein, I. D. 1955. Further observations on the treatment of superficial thrombophlebitis with phenylbutazone. Circulation. **12:** 833.
8. Stein, I. D. 1955. Inhibition of experimental venous thrombosis. Angiology. **6:** 403.

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